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Listerian Oration.[1]

HIGH BLOOD PRESSURE IN PREGNANCY.

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IT is a great honour to be included amongst the distinguished doctors who have been Listerian Orators, and I am deeply sensible of it. My predecessor and teacher, Professor Marshall Allan, was the orator in 1927, and his subject was "The Future of Obstetrics". A previous orator, Dr. Rothwell Adam, in 1922 had discussed the remarkable influence that the Listerian era had had on obstetrics in general and on puerperal infection in particular. Marshall Allan urged an obstetric revival based on a return to the high standards set by Lister. Today the miracle has happened—our maternal mortality has reached a record low level which we shall have difficulty in further reducing. Because of this I have to turn to less dramatic spheres of obstetrics from which to choose the subject of my address.

[1] Delivered at a meeting of the South Australian Branch of the British Medical Association on May 26, 1960.

This evening I wish to discuss the effects of pregnancy on mother and child in women with high blood pressure. In them pregnancy is known to be more dangerous, and until recent times termination of pregnancy by therapeutic abortion has often been advised.

The following criteria were laid down for the diagnosis of high blood pressure: (i) The blood pressure was to be 140/90 mm. of mercury or above; if either the systolic or diastolic pressure was below this level, the patient was not to be included. (ii) This level was to be reached before the end of the twentieth week of pregnancy and confirmed after the first visit to the hospital. A high level at the first visit only, not repeated before the twentieth week, was to exclude the patient. (iii) Patients with chronic pyelonephritis or chronic glomerulonephritis were to be excluded, even if the blood pressure conformed to the above-mentioned figures. The accepted criteria for a diagnosis of chronic renal disease were used.

In order to test the efficacy of the modern method of treatment of high blood pressure in pregnant women, it is proposed to compare a series consisting of patients who in 1956 were delivered at the Royal Women's Hospital, Melbourne, with a series of patients who were delivered in 1946-1947, and who would serve as controls. Two years are used so that the total number of patients is similar to that treated in 1956.

In 1946 and 1947, 8069 booked patients were delivered at the Royal Women's Hospital. In retrospect, 111 patients

presented themselves and satisfied those criteria for a diagnosis of high blood pressure set out above, an incidence of 1·3%. In 1956, 6866 booked patients were delivered. There were 109 patients who presented themselves with high blood pressure, an incidence of 1·6%.

During 1946 and 1947, the method of treating patients with high blood pressure was as follows. During pregnancy treatment was in the main ambulatory; there were comparatively few spare ante-natal beds available, and consequently these were reserved for patients with superimposed preeclampsia. At the first visit, a thorough examination was made and a decision taken to terminate or to carry on the pregnancy. Routine admission to hospital to assess the patient's cardio-vascular system was not undertaken. No special attention was paid to the diet, and the patient had the same care as other patients. No attempt was made to ensure regular ante-natal visits to the hospital. When preeclampsia occurred (as judged by the appearance of protein in the urine), or when the rise in blood pressure became excessive, the patient was admitted to hospital. In the absence of proteinuria, the blood pressure usually dropped with rest in bed, and if the patient was not near term, she was discharged from hospital; if she was near term, she remained in hospital to await the onset of labour. If proteinuria was present, treatment consisted of rest in bed, a diet of low protein content and restriction of fluids. If the proteinuria disappeared, the pregnancy was allowed to continue; if it persisted, however, labour was induced. This treatment conforms to that used in most obstetric centres of the world at that time. Treatment of patients with high blood pressure began to change in 1950, and gradually its present form evolved.

In 1956 the method of treating patients with high blood pressure was as follows. The patients were admitted to hospital to allow assessment of the cardio-vascular system. The cardiac size was estimated, the eye-grounds were checked, and the blood pressure at rest in bed was recorded. The urine was tested for protein, its specific gravity was noted and any sediment was examined. Such admission to hospital was possible in 1956, because we now had 60 ante-natal beds available. Some therapeutic abortions were carried out, the rest of the patients being left for detailed observation. In general, these patients realized that their blood pressures were under discussion, so that it was impossible to hide the reason for admission to hospital.

After a few days in hospital the blood pressure usually dropped; the patient was then allowed to get up, and after two or three days of walking around the ward, a decision whether to use hypotensive drugs was made. It was realized that on the patient's discharge from hospital the blood pressure would probably rise again to its previous level; therefore, any patient whose blood pressure during recumbency was 150/90 mm. of mercury or above after she had been ambulatory for two to three days was treated with hypotensive drugs straightaway. Thus 68 of the 101 patients were given "Serpasil" in the first trimester. The remaining 33 had blood pressures below 150/90 mm. of mercury, but some of them received hypotensive drugs in the third trimester.

"Serpasil" (reserpine), in a dosage of 0·25 mg. three times a day, was used to begin with. In the majority of cases this was usually effective; however, in some cases a dose of 0·5 mg. three times a day was required. The full effect was not obtained until two to three weeks from the commencement of treatment. There was a variability of effect; in some patients it was good, in others poor. The dosage was given as a matter of trial and error, as we were unable to predict which patient would show a good response and which would not. The drug had a prolonged action and had some sedative effect as well. In our experience, side effects were few. Mental depression has been described, but it was not seen in this group. A few patients complained of stuffiness in the nose. Gastro-intestinal symptoms were not seen, as pregnancy tends to lead to constipation.

The advantage of this drug is that postural hypotension rarely occurs, and it can be used with other hypotensive agents, especially the ganglion-blocking agents. When it is so used, the dosage of the ganglion-blockers can be reduced. The pharmacology of reserpine is not known; it is said to have a central action. After some days of treatment in hospital with hypotensive drugs, the blood pressure usually dropped below 150/90 mm. of mercury and the patient was discharged to the ante-natal clinic.

From the beginning of pregnancy, measures were taken to anticipate and prevent the development of preeclampsia. These were based on the work of Dixon Hughes (1951), of Hamlin (1952) and of Dawson (1953), and were as follows. (i) A regular check was made on weight gain during pregnancy. (ii) If the weight was over 140 lb., a protein-rich reduction diet of low sodium content was commenced from the outset of the pregnancy. This diet had a daily Calorie value of 1724 made up of 110 grammes of protein, 76 grammes of fat and 150 grammes of carbohydrate. (iii) If the patient weighed under 140 lb. the usual diet for pregnancy was allowed, but with no added salt with the meals. This diet contained 3000 Calories per day.

During pregnancy, the patient was admitted to hospital when (i) the blood pressure was above 150/90 mm. of mercury at the clinic, or (ii) the weight gain was above 3 lb. in four weeks, or three-quarters of a pound in one week.

About half of the patients were subsequently readmitted to hospital, and many had three or four admissions. Most of the patients who started pregnancy with a very high level were admitted to hospital at about 28 weeks and remained there. Rest in bed was an important method of treating the rise in blood pressure.

It was our experience that 0·75 mg. of "Serpasil" usually controlled the blood pressure in the first trimester, and that sometimes it was possible to reduce the dosage in the second trimester. In many patients, of whom some were receiving "Serpasil" and others not, the blood pressure tended to rise at or about the twenty-fourth week; if "Serpasil" had not been used, it was now commenced; for many who were taking "Serpasil", a ganglion-blocker ("Ansolysen") was necessary to control the rise.

"Ansolysen" (pentolinium tartrate) is a ganglion-blocking agent acting on both sympathetic and parasympathetic ganglia, producing a wide range of effects—namely, hypotension, intestinal ileus, gastric hyposecretion and capillary paralysis. In its action it resembles hexamethonium bromide, a drug with which we were familiar. It is about fifteen times as strong as hexamethonium bromide and its effects last longer. The test dose is always given with the patient standing up and the response is noted. The maximum effect is obtained two to three hours after the tablet has been taken. Any hypotensive symptoms such as dizziness can be relieved by lying or sitting down. Initially, 20 mg. of "Ansolysen" were given twice a day. The aim was to reduce the blood pressure in the recumbent position to below 150/90 mm. of mercury about two to three hours after the tablets had been taken. Most of the patients were taking "Serpasil", 0·25 mg. three times a day, as well. The dosage of "Ansolysen" was increased if a satisfactory response was not obtained. Sometimes we gave 20 mg. every six hours, or 40 mg. twice a day.

There were three disadvantages to the use of "Ansolysen". The first was the rapid tolerance developed to the drug, and the second was the constipating effect of the drug. When "Ansolysen" was combined with reserpine, this effect was reduced. The third was the postural hypotension that it produced. Postural hypotension is produced by venous pooling in the lower part of the body when the subject assumes the erect posture, with a subsequent decrease in cardiac output and a decrease in renal blood flow (Assali, 1954). This decrease in renal blood flow may be important if preeclampsia is present as well, since the renal blood flow is already reduced by arteriolar constriction. Morris (1957) has shown that,

TABLE I.
Patients in Both Series.

Initial Diastolic Blood Pressure in Millimetres of Mercury.	1956 Series.			1946 Series.		
	Number of Pregnancies.	Number of Therapeutic Abortions.	Number Delivered.	Number of Pregnancies.	Number of Therapeutic Abortions.	Number Delivered.
90–99	78	0	78	61	6	55
100–109	19	2	17	25	0	25
110 or more	12	6	6	25	13	12
Total	109	8	101	111	19	92

when the blood pressure in preeclampsia is reduced by hexamethonium, the myometrial blood flow is increased.

Usually the patients were in hospital to stabilize the blood pressure when "Ansolysen" therapy was commenced. The combination of "Ansolysen" and "Serpasil" was found to be particularly effective in pregnancy. In some patients with a high initial blood pressure, "Ansolysen" was used

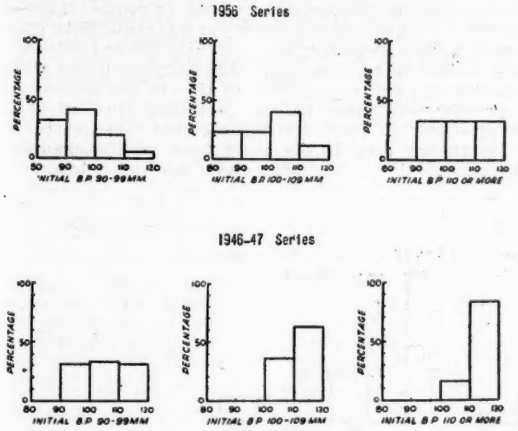

FIGURE I.
Blood pressure at the end of pregnancy compared with initial reading.

from the beginning of pregnancy. The level of blood pressure aimed at was one consistently below 150/90 mm. of mercury. If patients gained excessive weight during pregnancy, they were placed on the low-salt, high-protein, low-carbohydrate diet mentioned above, and if the weight gain continued or clinical œdema appeared, or if the blood pressure could not be kept below 150/90 mm. of mercury or proteinuria occurred, the patient was admitted or readmitted to hospital.

In some pregnancies spontaneous premature labour occurred; in others labour was induced because superimposed preeclampsia had failed to respond to treatment, or because the blood pressure could not be controlled. If the pregnancy was quite normal, it was allowed to proceed to term and the onset of spontaneous labour was awaited.

The indications for induction of labour need elaboration. In patients who were treated with hypotensive drugs, 37 weeks of gestation was the goal aimed for, as we considered the chances of a live baby to be particularly good then. If preeclampsia did not occur, the pregnancy was allowed to proceed; if there was an uncontrolled rise in the blood pressure above 150/90 mm. of mercury or if preeclampsia occurred and failed to respond to treatment, the pregnancy was terminated, no matter what the period of gestation. The indication for induction of labour when preeclampsia was superimposed was failure of the protein to disappear from the urine after adequate treatment. Anything more than a cloud in a catheter specimen was considered as a failure to clear.

In the 1956 series the following measures were in use to prevent (and perhaps, incidentally, to mask) the onset of preeclampsia. As soon as the weight gain became excessive (indicating occult œdema), the intake of salt was restricted to reduce the tendency to generalized œdema. The use of hypotensive drugs or an increase in their dosage prevented for a time an elevation in blood pressure. Unfortunately, when preeclampsia occurred in one of these cases there was very little therapy available, since most of the measures used in the routine treatment of preeclampsia had already been used prophylactically. Admission to hospital and bed rest were beneficial. The diuresis that occurred from assuming the horizontal position was usually very satisfactory. In addition, the patients were given 15 grains of ammonium chloride three times a day for three days, and a sedative if necessary.

Improvement was judged by fall in the blood pressure and a decrease in the amount of proteinuria. As long as a decrease in the amount of proteinuria was occurring, we were content to wait; when the decrease stopped, a decision whether to induce labour was made. Usually the blood pressure fall was satisfactory; but unless the protein practically disappeared from the urine, labour was induced.

RESULTS.

It is proposed to present the statistics using the height of the diastolic pressure at the initial visit as the common ground on which results may be compared. It is considered sound to compare the pregnancy, labour and fœtal outcome of two groups of patients with the same initial blood pressure, from 1946-1947 and from 1956. There are three groups according to the height of the initial diastolic blood pressures—namely, those with a pressure between 90 and 99, 100 and 109 and 110 or more millimetres of mercury. For ease of description, patients with an initial diastolic blood pressure of 90 to 99 mm. of mercury will be referred to as Group I, those with pressures of 100 to 109 mm. of mercury as Group II, and those with pressures of 110 mm. of mercury or more as Group III.

Maternal Results.

In the 1956 series, there were 109 patients and no maternal deaths. In the 1946-1947 series there were 111 patients and one maternal death. This was the death of a patient who had a therapeutic abortion for malignant hypertension. She died on the tenth day after operation from cerebral hæmorrhage.

In 1956, eight therapeutic abortions were carried out, two in Group II and six in Group III (Table I).

In 1946-1947, 19 pregnancies were therapeutically aborted. There were six terminations in Group I and 13 in Group III.

TABLE II.

Fatal Outcome in Relation to Mid-Pregnancy Fall in Blood Pressure, 1946–1947 Series.

Initial Diastolic Blood Pressure. (Mm. of Mercury.)	Proteinuria.	No Fall.		Fall of 10 mm.		Fall of 11–20 mm.		Fall of 21 mm. or More.		Total with Fall.	
		Number.	Perinatal Mortality.	Number.	Perinatal Mortality.	Number.	Perinatal Mortality.	Number.	Perinatal Mortality.	Number.	Perinatal Mortality.
90–99	None.	26	2	7	—	6	—	—	—	13	—
	Some.	15	2	2	—	—	—	—	—	2	—
100–109	None.	12	3	5	—	2	—	—	—	7	—
	Some.	6	2	1	—	—	—	—	—	1	—
110 or more	None.	1	—	2	—	1	—	2	—	5	—
	Some.	3	—	2	—	1	1	—	—	3	1
Total	None.	39	5	14	—	9	—	2	—	25	—
	Some.	24	4	5	—	1	1	—	—	6	1
Grand total ..	.. ..	63	9	19	—	10	1	2	—	31	1

Control of the Blood Pressure.

In the 1956 series, Figure I illustrates the change in the blood pressure during the pregnancy. When the height of the blood pressure at the end of pregnancy is compared with the initial level, in Group III most success was achieved, as no patient showed a rise; in Group II there was a rise of 10 mm. in 12% of cases, whereas in Group I there was a rise of 10 mm. in 10% of cases and a rise of 20 mm. in 6%.

In the 1946-1947 series, Figure I illustrates that in Group III, 16% of patients showed a fall of 10 mm. and 84% showed no change. In Group II, 36% showed no change and 64% a rise of 10 mm. In Group I, none showed a fall in pressure, 32% showed no change, 34% showed a rise of 10 mm., and 32% showed a rise of 20 mm.

Comparing the two series each to each, or comparing each initial blood pressure group in each series, there is a statistical significance in the fall in blood pressure towards the end of pregnancy in the 1956 series as compared with the 1946-1947 series.

Many workers have commented on the mid-pregnancy drop in blood pressure, which is a phenomenon of normal pregnancy, and which, in patients with high blood pressure, may become exaggerated. Owing to the use of hypotensive drugs in the 1956 series, a drop occurred soon after these were used, and it has been impossible to ascertain whether this fall was exaggerated or not by the so-called natural fall. We did notice that during the second trimester we were often able to reduce the dose of hypotensive agent in many cases.

We wish to present the 1946-1947 series as evidence of the mid-pregnancy fall in blood pressure, because in those years no specific measures were used to reduce the blood pressure in the second trimester. In all, 31 patients (33%) showed a mid-pregnancy drop. Table II and Figure II show the fall in blood pressure that occurred in the middle trimester and the relationship of this to the development of preeclampsia later in the pregnancy in each blood pressure group. They demonstrate that when there is a mid-pregnancy drop in the blood pressure, the chances of subsequently developing proteinuria are much less.

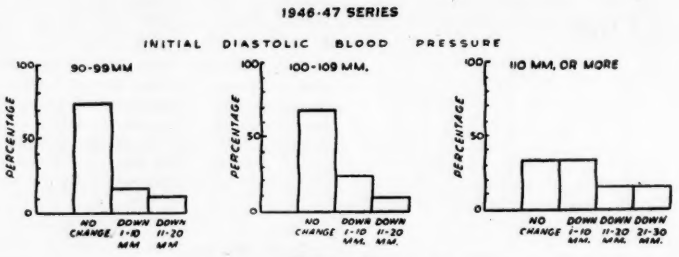

FIGURE II.

Mid-pregnancy drop in blood pressure.

Significant Proteinuria.

Significant proteinuria was taken to mean anything more than a trace of albumin in a catheter specimen of urine after boiling.

From the beginning of the present experiment, it has been evident that superimposed preeclampsia alters the prognosis for the fœtus.

In Figure III the incidence of proteinuria is shown in percentages according to the blood pressure at the beginning of the pregnancy in both series. Comparing the 1956 series with the 1946-1947 series, in Group I it was 24% and 31% respectively, in Group II it was 12% and 24% respectively, in Group III it was 33% and 50% respectively, and for the whole series it was 23% and 32% respectively.

In 1956, the over-all incidence of proteinuria among all patients admitted to the hospital was 5%, and the incidence in the high blood pressure group was 23%; this indicated that a rise in the initial diastolic blood pressure increased the incidence of proteinuria. It might be expected that the incidence of proteinuria would increase the higher the initial blood pressure; but, as the initial blood pressure

rises from 90 to 99 mm. through to 110 mm. or more, the incidence of proteinuria does not continue to rise.

The correlation between initial height of blood pressure and incidence of proteinuria is seen better in the 1946-1947 series, in which it was more or less the same in Groups I and II—namely, 30% and 27%—and then rose to 50% in Group III. As no measures were taken to prevent preeclampsia in this series, these results are a better indication of the occurrence of proteinuria. It can be concluded that the incidence of proteinuria in each

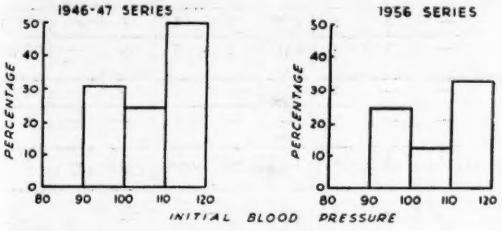

FIGURE III.
Incidence of superimposed proteinuria.

series is higher than in patients with an initial blood pressure below 140/90 mm. of mercury, and that in the 1946-1947 series, with rises in blood pressure above 140/90 mm. of mercury, the incidence of increased proteinuria tends to rise the higher the initial diastolic blood pressure is over 90 mm. In the 1956 series there is no correlation in the lower blood pressure groups.

As there is a big increase in the incidence of proteinuria in the group with a diastolic blood pressure of 90 mm. and above as compared with the whole range of the hospital population, it is reasonable to assume that the incidence of proteinuria in the group with a blood pressure of 80 to 89 mm. of mercury is probably higher than in the group with a blood pressure of 70 to 79 mm.

Induction of Labour.

In 1956, 67% of the patients had labour induced for reasons that have already been defined. In the 1946-1947 series, induction of labour was performed in 55% of cases. Figure IV shows the indications for induction of labour in the two series according to the initial blood pressures.

There has been an over-all increase in the number of inductions in the 1956 series. The inductions for proteinuria have dropped from 25% in the 1946-1947 series to 18%. If the number of inductions for proteinuria is considered according to the initial blood pressure readings, the incidence of induction has been reduced in each group when compared with the 1946-1947 series, because the incidence of proteinuria has dropped. It will be shown

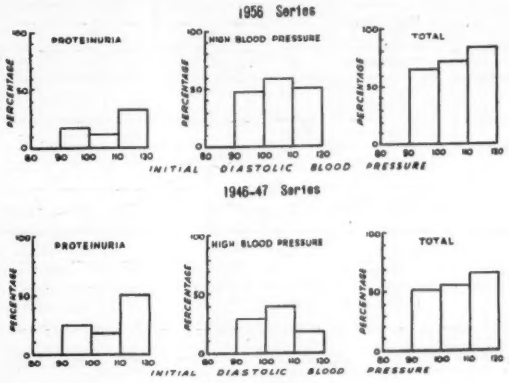

FIGURE IV.
Fœtal wastage.

later that the time at which proteinuria appears has been delayed in the 1956 series. If the number of inductions of labour for high blood pressure is considered, there has been an increase. It rose from 30% in the 1946-1947 series to 50% in the 1956 series. This illustrates that the policy of induction when the pregnancy reaches 37 weeks has been carried out in the 1956 series. As was stated previously, this was not so in the 1946-1947 series.

Tables III and IV show the period of gestation and the reason for induction of labour when it was carried out according to the initial blood pressure. In addition, the perinatal mortality following induction is noted. In the 1956 series, in Group I there was one induction for high blood pressure before the thirty-seventh week; there were 14 inductions for proteinuria. In Group II there was one induction for proteinuria before the thirty-seventh week,

TABLE III.
Period of Gestation when Labour Induced—1956 Series.[1]

Initial Diastolic Blood Pressure. (Mm. of Mercury.)	Reason for Induction.	Weeks.											Total.
		32	33	34	35	36	37	38	39	40	41	42	
90–99	High blood pressure.	—	—	—	—	1	2	6	6	17	2	3	37
	Proteinuria.	1	—	1 (1)	1 (1)	1	5 (1)	3	1	1	—	—	14 (3)
100–109	High blood pressure.	—	—	—	—	1	2	4	1	1	1	—	10
	Proteinuria.	—	—	—	1 (1)	—	—	1	—	—	—	—	2 (1)
110 or more	High blood pressure.	—	—	—	—	—	1	—	—	1	1	—	3
	Proteinuria.	1 (1)	—	—	—	—	—	1	—	—	—	—	2 (1)
Total	High blood pressure.	—	—	—	—	2	5	10	7	19	4	3	50
	Proteinuria.	2 (1)	—	1 (1)	2 (2)	1	5 (1)	5	1	1	—	—	18 (5)
Grand total	.. ..	2 (1)	—	1 (1)	2 (2)	3	10 (1)	15	8	20	4	3	68 (5)

[1] Figures in parentheses refer to perinatal mortality.

TABLE IV.

Period of Gestation when Labour Induced—1946–1947 Series.[1]

Initial Diastolic Blood Pressure. (Millimetres of Mercury.)	Reason for Induction.	Pre-viable.	Weeks.															Total.
			28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	
90–99 ..	High blood pressure.	—	—	—	—	—	—	—	—	—	2	—	3	4	6	—	1	16
	Proteinuria	—	—	—	—	—	1 (1)	—	—	—	3	2	2	2	3	—	—	13 (1)
100–109 ..	High blood pressure.	1 (1)	—	—	—	—	—	—	—	—	1	1	3 (1)	1	3	—	—	10 (2)
	Proteinuria	1 (1)	—	—	—	—	—	—	1	—	—	1	1	—	—	—	—	4 (1)
110 or more	High blood pressure.	—	—	—	—	—	—	—	—	—	—	1	—	—	1	—	—	2
	Proteinuria	—	—	—	—	—	2	1	—	1	1	—	1 (1)	—	—	—	—	6 (1)
Total ..	High blood pressure.	1 (1)	—	—	—	—	—	—	—	—	3	2	6 (1)	5	10	—	1	28 (2)
	Proteinuria	1 (1)	—	—	—	—	3 (1)	1	1	1	4	3	4 (1)	2	3	—	—	23 (3)
Grand total	.. ..	2 (2)	—	—	—	—	3 (1)	1	1	1	7	5	10 (2)	7	13	—	1	51 (5)

[1] Figures in parentheses refer to perinatal mortality.

TABLE V.

Results of Induction of Labour—1956 Series.[1]

Indication.	Method.	Diastolic Blood Pressure at the Beginning of the Pregnancy.			Total Number of Patients Induced.	Result.	
		90 to 99 mm.	*100 to 109* mm.	*110* mm. or More.		Vaginal Delivery.	Cæsarean Section.
Proteinuria	Artificial rupture of membranes.	13 (2)	2 (1)	2 (1)	17	17 (4)	—
	Elective Cæsarean section.	1 (1)	—	—	1	—	1 (1)
High blood pressure..	Artificial rupture of membranes.	37 (0)	9 (0)	2 (0)	48	45 (0)	3 (0)
	Elective Cæsarean section.	—	1 (0)	1 (0)	2	—	2 (0)
Total ..	.. .. ..	51 (3)	12 (1)	5(1)	68	62 (4)	6 (1)

[1] Figures in parentheses refer to perinatal mortality.

TABLE VI.

Results of Induction of Labour—1946–1947 Series.[1]

Indication.	Method.	Diastolic Blood Pressure at the Beginning of the Pregnancy.			Total Number of *Patients* Induced.	Result.	
		90 to 99 mm.	100 to 109 mm.	110 mm. or More.		Vaginal Delivery.	Cæsarean Section.
Proteinuria	Artificial rupture of membranes.	13 (0)	3 (1)	4 (1)	20	18 (2)	2 (0)
	Elective Cæsarean section.	—	1 (0)	2 (0)	3	—	3 (0)
High blood pressure	Artificial rupture of membranes.	15 (0)	9 (2)	1 (0)	25	24 (2)	1 (0)
	Elective Cæsarean section.	1 (0)	1 (0)	1 (0)	3	—	3 (0)
Total ..	.. .. ..	29 (0)	14 (3)	8 (1)	51	42 (4)	9 (0)

[1] Figures in parentheses refer to perinatal mortality.

TABLE VII.
Summary of Pregnancies—1956 Series.

Initial Diastolic Blood Pressure in Millimetres of Mercury.	Number of Pregnancies.	Number Delivered.	Number of Therapeutic Abortions.	Unsuccessful Pregnancies.					Total Wastage.
				Previable Deaths (Abortions).	Stillbirths.	Neonatal Deaths.	Perinatal Mortality.	Corrected Perinatal Mortality.	
90–99	78	78	0	0	2	3	5	3	5
100–109..	19	17	2	0	0	2	2	1	4
110 or more	12	6	6	0	1	0	1	1	7
Total	109	101	8	0	3	5	8	5	16

and one for high blood pressure. In Group III there was one induction for proteinuria before the thirty-seventh week. This made a grand total of eight inductions of labour (including four fœtal deaths) before 37 weeks. In the 1946-1947 series, in Group I there were two inductions for high blood pressure and four for proteinuria. In Group III there were no inductions for high blood pressure and five for proteinuria. This made a grand total of 15 inductions (with a perinatal mortality of three).

As the appearance of significant proteinuria was an indication for induction of labour, it follows that the period of gestation when labour was induced for proteinuria will give an indication as to the stage of pregnancy at which preeclampsia is developing. In the 1956 series there were six inductions for preeclampsia before the thirty-seventh week; in the 1946-1947 series there were 11. There is therefore a delay in the time of devlopment of preeclampsia in the 1956 series.

Tables V and VI show the results of the induction of labour. In all cases in both the 1956 series and the 1946-1947 series, when a decision was made to induce labour, only two methods were used; these were artificial rupture of the membranes and elective Cæsarean section. Rupture of the forewaters was used exclusively, no matter what the state of the cervix or station of the head. If labour had not commenced in 24 hours, a medical induction with divided intramuscular doses of pituitrin was used. Failure to come into labour within 48 hours was an indication for Cæsarean section.

In the 1956 series, 18 patients underwent induction for preeclampsia. Of these, one had an elective Cæsarean section. Fifty patients underwent induction for high blood pressure, two had an elective Cæsarean section, and 48 had labour induced by artificial rupture of the membranes; of the last group, three failed to come into labour and were delivered by Cæsarean section. In the 1946-1947 series, of the 23 patients who had labour induced because of preeclampsia, three had an elective Cæsarean section and 20 an artificial rupture of the membranes; of the latter group, two failed to come into labour and were delivered by Cæsarean section. Of the 28 who had labour induced for high blood pressure, three had an elective Cæsarean section and 25 an artificial rupture of the membranes; one of these failed to come into labour and was delivered by Cæsarean section. The elective Cæsarean section rate in the 1956 series was 4% and in the 1946-1947 series 12%.

In the 1956 series, 5% of patients failed to come into labour after an artificial rupture of the membranes; in the 1946-1947 series there was a 7% failure rate. The efficacy of artificial rupture of the membranes as a method of induction of labour is shown in both series, especially if the reason for induction was proteinuria. The method is also safe for the fœtus, as in the 1956 series the perinatal mortality in the group who had labour induced by artificial rupture of the membranes was 6%; it was 8% for the whole series. In the 1946-1947 series, the perinatal mortality in the labour-induced group was 10%; it was 11% for the whole series.

Fœtal Results.

Perinatal Mortality.

Table VII gives a summary of all the pregnancies in the 1956 series according to the initial diastolic blood pressure. There were four sets of twins. The over-all fœtal wastage was 16 (15%). This includes therapeutic abortions, spontaneous abortions, still-births and neonatal deaths. (For this investigation, spontaneous abortions, still-births and neonatal deaths that occurred before discharge from hospital are included in the perinatal mortality.) The perinatal mortality was eight (8%). The perinatal mortality (excluding abortions) at the Royal Women's Hospital in 1956 for all booked patients was 1·9% (still-births 1·1%, neonatal deaths 0·8%).

For the purpose of comparison of the two series, it is proposed to correct the fœtal mortality by eliminating the three deaths due to congenital abnormalities, giving a corrected figure of five (5%).

Table VIII gives a summary of the pregnancies in the 1946-1947 series. There were two sets of twins. The over-all fœtal wastage was 29 (26%). The perinatal mortality was ten (11%).

TABLE VIII.
Summary of Pregnancies—1946–1947 Series.

Initial Diastolic Blood Pressure in Millimetres of Mercury.	Number of Pregnancies.	Number Delivered.	Number of Therapeutic Abortions.	Unsuccessful Pregnancies.				Total Wastage.
				Previable Deaths (Abortions).	Stillbirths.	Neonatal Deaths.	Perinatal Mortality.	
90–99	61	55	6	0	4	0	4	10
100–109	25	25	0	3	1	1	5	5
110 or more	25	12	13	0	1	0	1	14
Total	111	92	19	3	6	1	10	29

As there were no congenital abnormalities in the 1946-1947 series, the corrected mortality rate remains the same as the uncorrected—namely, 10 (11%).

Figure V shows a comparison of the fœtal wastages for the 1956 series and the 1946-1947 series, tabulated according to the initial diastolic blood pressure. It is clearly seen from both series that the chance of a live child decreases as the initial blood pressure rises.

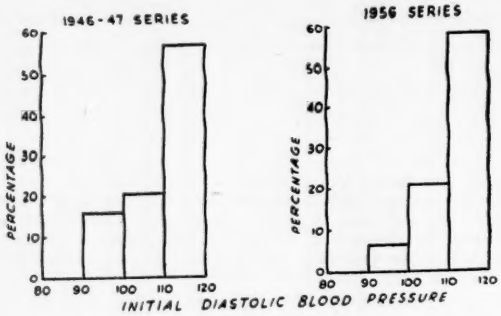

FIGURE V.
Rates of induction of labour.

Perinatal Mortality and the Initial Diastolic Blood Pressure.

Figure VI shows the perinatal mortality in relation to the initial diastolic blood pressure. In the 1956 series there were 105 babies. All the twins were born to patients in Group I. In Group I, the mortality rate was 6%, in Group II it was 12% and in Group III it was 16%.

In the 1946-1947 series, the loss in Group I was 7%, in Group II it was 19% and in Group III it was 8%.

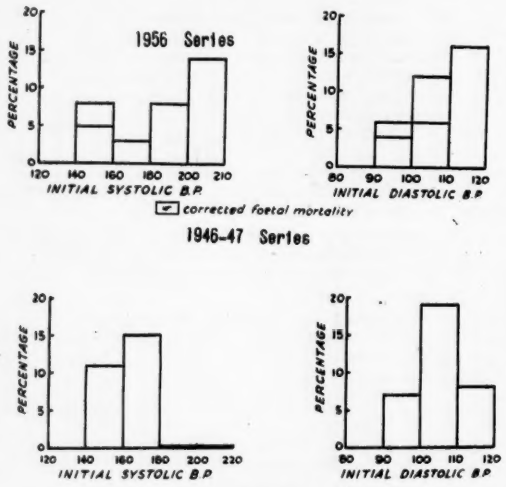

FIGURE VI.
Perinatal mortality.

Figure VII shows the corrected perinatal mortality in relation to the initial diastolic blood pressure. When the corrected mortality for each group of the two series is compared, there is an improvement in the perinatal mortality in Group I and II for 1956 as compared with the 1946-1947 series. In Group III the 1946-1947 series is better. In the 1956 series, the corrected and uncorrected perinatal mortality increases the higher the initial diastolic pressure. This is also shown in the 1946-1947 series except for Group III.

In the 1956 series, of the 78 patients whose diastolic blood pressure was 90 to 99 mm. of mercury, the corrected perinatal mortality rate was 4%. In the whole hospital the perinatal mortality rate was a little under 2%. In fact, the risk to the fœtus in this blood-pressure group is not much greater than when the blood pressure is below 90 mm. When the initial blood pressure rises, so does the risk to the fœtus. This indicates that there is a gradual rise in the perinatal mortality as the initial blood pressure rises, and that it is impossible to select a level and say "above this level is dangerous".

In the present investigation the level of 90 mm. of mercury was selected; but from the results it is clear that this was arbitrary, and that Pickering's views hold for patients with the blood pressures that are found in pregnancy—that is, that there is no dividing line between the normal and abnormal; it is one population, and the patients with a high level are merely the right-hand side of a distribution curve, the difference being quantitative and not qualitative. It is the relative rise in blood pressure that is important.

Perinatal Mortality and Proteinuria in the Mother.

Tables IX and X show the perinatal mortality in relation to proteinuria. In the series as a whole, the risk to

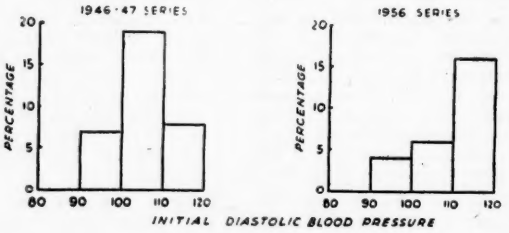

FIGURE VII.
Corrected perinatal mortality.

the fœtus when proteinuria develops is clearly shown. In the 1956 series, the corrected perinatal mortality among the 78 patients with no proteinuria is nil, and among the 23 who developed proteinuria it is five (22%). In the 1946-1947 series, among the 63 with no proteinuria it is five (8%), and among the 29 who developed proteinuria it is five (17%).

In the 1956 series (as shown in Figure VIII), when the initial diastolic blood pressures, the development of proteinuria and the corrected perinatal mortality are considered, we find that in Group I, with no proteinuria the mortality rate is nil, and with proteinuria it is 14%. In Group II with no proteinuria it is nil, and with proteinuria 50%. In Group III with no proteinuria it is nil, and with proteinuria 50%. In the 1946-1947 series (as shown in Figure IX), in Group I the corresponding figures are 5% and 12%, in Group II 16% and 29%, and in Group III nil and 16%. These statistics show that the risk to the fœtus increases when proteinuria develops, and that this risk is greater when it develops in patients with a higher initial blood pressure.

In Table II, the incidence of superimposed toxæmia, the perinatal mortality and the fall in the blood pressure in mid-pregnancy are shown for the 1946-1947 series. When no proteinuria develops, a fall in blood pressure is favourable to the fœtal prognosis; in 25 with a fall there is no fœtal loss, whereas with 39 with no fall the loss is five. When proteinuria occurs, the fœtal loss is the same (16%) if a fall occurs or not. Thus a mid-pregnancy fall is favourable to the fœtus provided proteinuria does not subsequently occur.

To summarize this discussion on fœtal outcome in relation to proteinuria in the mother, we have found: (i) In each series the risk to the fœtus is increased when proteinuria occurs. (ii) When proteinuria occurs, the risk

TABLE IX.

Fœtal Outcome in Relation to Blood Pressure—1956 Series.[1]

Initial Diastolic Blood Pressure in Millimetres of Mercury.	Proteinuria near Delivery.	Diastolic Blood Pressure near Delivery.										Grand Total.	
		Under 90 mm.		90 to 99 mm.		100 to 109 mm.		110 or More.		Total.			
		Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.
90–99 ..	None ..	27	2 (0)	21	0 (0)	9	0 (0)	3	0 (0)	60	2 (0)	82	5 (3)
	Some ..	—	—	13	1 (1)	7	1 (1)	2	1 (1)	22	3 (3)		
100–109 ..	None ..	4	0 (0)	4	0 (0)	5	0 (0)	2	1 (0)	15	1 (0)	17	2 (1)
	Some ..	—	—	—	—	2	1 (1)	—	—	2	1 (1)		
110 or more	None ..	—	—	2	0 (0)	2	0 (0)	—	—	4	0 (0)	6	1 (1)
	Some ..	—	—	—	—	—	—	2	1 (1)	2	1 (1)		
Total ..	None ..	31	2 (0)	27	0 (0)	16	0 (0)	5	1 (0)	79	3 (0)	105	8 (5)
	Some ..	—	—	13	1 (1)	9	2 (2)	4	2 (2)	26	5 (5)		
Grand total ..		31	2 (0)	40	1 (1)	25	2 (2)	9	3 (2)	105	8 (5)		

[1] Figures in parentheses refer to corrected perinatal mortality.

to the fœtus is greater the higher the initial diastolic pressure. (iii) A mid-pregnancy fall in blood pressure is favourable only if proteinuria does not subsequently develop.

DISCUSSION.

Maternal Prognosis.

The immediate prognosis for the mother in both series presented is good. No pregnancy in a patient with malignant hypertension was carried on, and with this exception it must be concluded that pregnancy is safe for the mother no matter what the original blood pressure is. There were no maternal deaths in the 1956 series and one in the 1946-1947 series, an incidence of 0·5% in the combined series. The over-all maternal mortality rate in the hospital for all booked patients was nil in 1956 and 0·15% in 1946-1947. The risk of pregnancy for most of these patients with high blood pressure is no greater than the risk for all patients. However, the late prognosis may be less favourable if there is any residual elevation in blood pressure *post partum*. The one maternal death in the two series occurred as a result of a procedure which it was thought would prolong her life. She had malignant hypertension.

When the number of therapeutic abortions in each series is considered, statistical analysis shows that there is a highly significant reduction in the number of therapeutic abortions in the 1956 series as compared with the 1946-1947 series (Figure X).

If the rates of therapeutic abortion are studied according to initial blood pressure, in Group I the rate changed from 10% to nil, in Group II it changed from nil to 11%, and in Group III it remained at 50%. A noteworthy change is that in the lowest blood-pressure group there were no terminations in the 1956 series; six were done in the 1946-1947 series and are very hard to justify; the pro-

TABLE X.

Fœtal Outcome in Relation to Blood Pressure—1946–1947 Series.

Initial Diastolic Blood Pressure in Millimetres of Mercury.	Proteinuria near Delivery.	Diastolic Blood Pressure near Delivery.										Grand Total.	
		Under 90 mm.		90 to 99 mm.		100 to 109 mm.		110 or More.		Total.			
		Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.	Number of Babies.	Perinatal Mortality.
90–99 ..	None ..	—	—	14	—	16	2	9	—	39	2	56	4
	Some ..	—	—	4	—	4	—	9	2	17	2		
100–109 ..	None ..	—	—	—	—	8	1	11	2	19	3	26	5
	Some ..	—	—	—	—	1	—	6	2	7	2		
110 or more	None ..	—	—	—	—	2	—	4	—	6	—	12	1
	Some ..	—	—	—	—	—	—	6	1	6	1		
Total ..	None ..	—	—	14	—	26	3	24	2	64	5	94	10
	Some ..	—	—	4	—	5	—	21	5	30	5		
Grand total ..		—	—	18	—	31	3	45	7	94	10		

cedure has now been abandoned. Is it true to say that there has, in fact, been no change in policy, and that the reduction is due to the fact that in the 1956 series the number of patients presenting in Group III is reduced?

We consider that the statistically significant reduction in the number of therapeutic abortions is due to a more conservative attitude regarding abortion, and, further, that nowadays not many women with diastolic blood pressures of 110 mm. of mercury or more are becoming pregnant. There were 10 therapeutic abortions for high blood pressure in 1957. This is a similar percentage to 1956 and is in keeping with the trend already mentioned—

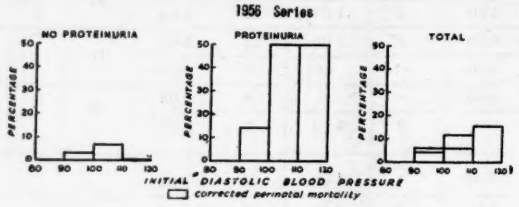

FIGURE VIII.
Perinatal mortality.

that is, that malignant hypertension is the only absolute indication. If this had been the only indication in both series, the number of cases in which abortions were performed would have been three in 1946-1947 and two in 1956.

Another factor concerning therapeutic abortion which has not been discussed is the difficulty of inducing patients aged 35 to 40 years to come into hospital for most of the pregnancy when there is a family of four or five to look after at home.

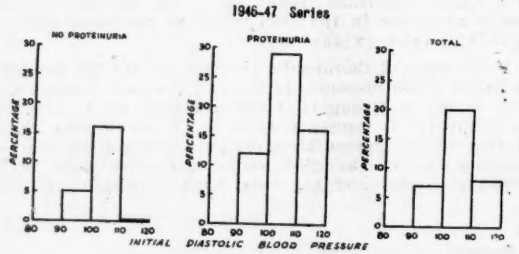

FIGURE IX.

The patients in these series were all of the "public hospital" type, with no help at home, and it was often impossible for them to cooperate even if they wanted to; for this reason the obstetricians must have thought that pregnancy was a risk under such conditions, especially if the blood pressure has risen during pregnancy and if preeclampsia occurs before fœtal viability.

Given ideal conditions for treatment, the only indication for termination of pregnancy is the presence of malignant hypertension. In these circumstances, the prognosis for the mother is already poor and the chance of a successful pregnancy very remote.

Therapeutic Lowering of the Blood Pressure.

It has been shown statistically that the percentage of patients with levels of diastolic pressure lower at the end of pregnancy than at the beginning has been increased over the decade. This can have several explanations. The use of bed rest and hypotensive drugs can be given the credit. Another possibility is that, because rise in blood pressure is also a sign of preeclampsia, measures to prevent the occurrence of this condition will successfully reduce the number of patients who show a rise in blood pressure. There will be no attempt to decide which of these three factors is the most important; suffice it to say that a substantial decrease has been achieved.

The fact that this decrease was not obtained in all cases can be due to the ineffectiveness of either the measures to prevent preeclampsia or the hypotensive drugs. We have already noted how varied is the response to hypotensive drugs in different individuals. It is not our intention to advocate one hypotensive agent as being superior to another. It is the fall in blood pressure that is important. We do not know whether the hypotensive agents have any effect in preventing preeclampsia, but we know that they will reduce blood pressure even when that condition is present, provided that a suitable agent is used. Townsend (1955) demonstrated this using hexamethonium bromide in the treatment of imminent eclampsia. The ideal hypotensive drugs has yet to be found; the search continues for an agent which will give more consistent results, especially during labour.

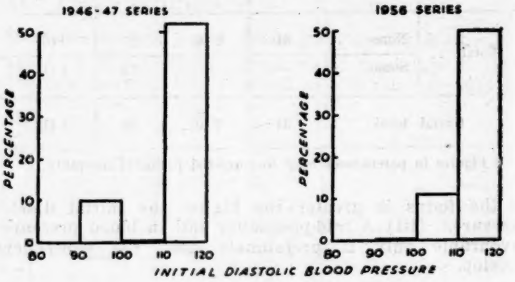

FIGURE X.
Termination of pregnancy.

The success of the measures adopted in the 1956 series to reduce the initial blood pressure was greater in the higher levels, as might have been expected. In Group III, 66% showed a fall, in Group II 48% and in Group I 33%. It is opportune at this point to mention that we are using hypotensive agents at blood-pressure levels that our medical colleagues would consider unsuitably low for such therapy. The advantage we have is that therapy is not prolonged, and that tolerance to the drug is not a great problem; once the pregnancy is over, the use of the drug may be discontinued.

We are aiming at diastolic blood pressure levels of under 90 mm. of mercury. Another important point is that blood pressure levels on their own are not important, for in the absence of proteinuria they are not significant when fœtal statistics are being discussed. It is the rise or fall that is important.

Significance of the Systolic and Diastolic Readings.

When the clinical portion of this study was being carried out, it was the intention to present the material using the initial systolic blood pressure; this was because the current practice at the hospital was to determine treatment according to the height of the systolic rather than the diastolic blood pressure.

Table XI shows a summary of the pregnancies prepared with the systolic blood pressure as the basis of the presentation. Four groups are used: 140-159 mm., 160-179 mm., 180-189 mm., 200 mm. or more. Table XII shows a similar presentation for the 1946-1947 series. Figures XI and XII show the uncorrected and corrected perinatal mortalities, the initial diastolic and systolic blood pressures being severally used as a basis.

In the 1956 series (Figure XI), with the initial diastolic pressure used in the way described, the corrected perinatal mortality rate is 4%, 6% and 16% as the blood pressure increases. When the systolic pressures are used it is 5%, nil, 8% and 14%. Thus, using the diastolic pressure, we

TABLE XI.

Summary of Pregnancies—1956 Series.

Initial Systolic Blood Pressure in Millimetres of Mercury.	Number of Pregnancies.	Number Delivered.	Number of Therapeutic Abortions.	Unsuccessful Pregnancies.					Total Wastage.
				Previable Deaths.	Stillbirths.	Neonatal Deaths.	Perinatal Mortality.	Corrected Perinatal Mortality.	
140 to 159	61	61	—	—	2	3	5	3	5
160 to 179	29	28	1	—	—	1	1	—	2
180 to 200	12	7	5	—	—	1	1	1	6
200 or more	7	5	2	—	1	—	1	1	3
Total	109	101	8	—	3	5	8	5	16

find a gradual increase in the perinatal mortality rate as the initial blood pressure increases; when the systolic pressures are used, no such change is found. Such a conclusion has been reached before, as far as systolic levels are concerned, but this was not confirmed in the present series.

In the 1946-1947 series (Figure XII), for diastolic pressures the perinatal mortality rate is 7%, 19% and 8%, and for systolic pressures it is 11%, 15%, nil and nil.

TABLE XII.

Summary of Pregnancies—1946-1947 Series.

Initial Systolic Blood Pressure in Millimetres of Mercury.	Number of Pregnancies.	Number Delivered.	Number of Therapeutic Abortions.	Previable Deaths.	Stillbirths.	Neonatal Deaths.	Perinatal Mortality.	Total Wastage.
140 to 159	49	46	3	1	3	1	5	8
160 to 179	34	32	2	1	4	—	5	7
180 to 200	19	12	7	—	—	—	—	7
200 or more	9	2	7	—	—	—	—	7
Total	111	92	19	2	7	1	10	29

Thus, neither the systolic nor the diastolic readings at the first visit show a correlation with the perinatal mortality figures.

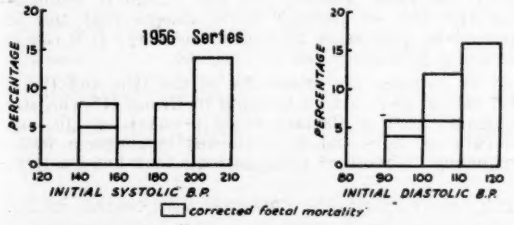

FIGURE XI.
Perinatal mortality.

Using the systolic pressures, we come to the conclusion that the height of the initial blood pressure gives little information as to the outcome of pregnancy in either series. However, when diastolic pressure is used, there is a definite trend seen in the 1956 series—namely, that the higher the initial pressure, the worse the prognosis for the fœtus. We have found taking the diastolic pressure more satisfactory, as it shows less tendency to variation, except for the few times when the sounds are difficult to interpret.

Most published reports have used the systolic blood pressure for the statistical analyses. We advocate the diastolic pressures as being more reliable to measure and of greater prognostic significance.

Prevention of Proteinuria.

We have already stated why it would be very difficult in the 1956 series to determine how many patients developed preeclampsia. That is why the term "significant proteinuria" is used. In the 1946-1947 series, a reliable figure could be produced, for we have records of all patients who showed generalized œdema or a relative rise in blood pressure or proteinuria, and therapy did not mask the development of any of them. Instead we are going to compare the incidence of proteinuria in the two

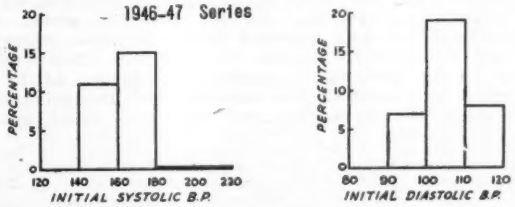

FIGURE XII.

series; this amounts to a consideration of incidence of moderate or severe preeclampsia, because, in most patients with preeclampsia, œdema and a rise in blood pressure occur initially, and at this stage the disease is often termed mild; when proteinuria appears, the condition is classified as moderate or severe; by definition other causes of proteinuria are excluded.

To judge from the initial diastolic blood pressure groups, there is a decrease in the incidence of proteinuria on comparison of the two series (Figure III). The difference is not statistically significant, both when the series is taken as a whole and in each initial blood pressure group. The difference is especially so in Groups II and III. Such

TABLE XIII.
Period of Gestation when Delivered—1956 Series.[1]

Initial Diastolic Blood Pressure in Millimetres of Mercury.	Weeks.												Total.
	Under 32	32	33	34	35	36	37	38	39	40	41	42	
90 to 99	—	2 (0)	—	1 (1)	1 (1)	7 (1)*	9 (1)	13 (0)	11 (0)	29 (0)	3 (0)	6 (1)*	82 (5)**
100 to 109	—	—	—	—	1 (1)	1 (0)	3 (0)	6 (1)*	1 (0)	3 (0)	2 (0)	—	17 (2)*
110 or more	—	1 (1)	—	—	—	—	1 (0)	1 (0)	—	2 (0)	1 (0)	—	6 (1)
Total	—	3 (1)	—	1 (1)	2 (2)	8 (1)*	13 (1)	20 (1)*	12 (0)	34 (0)	6 (0)	6 (1)*	105 (8)***

[1] Figures in parentheses refer to perinatal mortality. Each asterisk (*) denotes one case of congenital abnormality.

a decrease may be related to the improved lowering of blood pressure that can be effected in these two groups by rest and hypotensive agents. The incidence of proteinuria tends to rise as the initial blood pressure rises, and there is no doubt that if the blood pressure falls during pregnancy the incidence of proteinuria is decreased. Of the 23 patients in the 1956 series who developed proteinuria, only two (9%) did so before the thirty-seventh week; in the 1946-1947 series, only seven of the 29 did (24%). This shows that the time of appearance of proteinuria has been delayed. This is very important, especially when we consider that induction of labour is carried out when proteinuria persists despite treatment.

It has been held by most authors that it is impossible to forecast which patient will develop proteinuria. It is of great importance to be able to know, since the supervention of this sign increases the risk to the fœtus. There are two methods whereby the improbability of this complication can be forecast: (i) If there is a mid-pregnancy drop of 10 mm. in the diastolic blood pressure, the chances of development of proteinuria are reduced. If there is a mid-pregnancy drop of 20 mm. in the blood pressure, the chances that it will develop are very small. (ii) If the diastolic blood pressure during the third trimester is below the initial blood-pressure level, proteinuria will rarely occur.

Prolongation of Pregnancy.

Table XIII shows the period of gestation at which delivery took place in the 1956 series. The table also shows the perinatal mortality, corrected and uncorrected. Table XIV shows the results for the 1946-1947 series.

It was the aim in the 1956 series to prolong the pregnancy until the thirty-seventh week, by which time it was considered that the risks to the baby if delivered were practically non-existent. In the 1946-1947 series, 20 patients (22%) were delivered before 37 weeks, whereas in the 1956 series the number was 12 (12%). This reduction is not statistically significant. As far as fœtal survival is concerned, the importance of prolonging the pregnancy is well known, and the more recent series exemplifies this.

Of those babies delivered before 37 weeks, five of the 21 in the 1946-1947 series did not live (24%); in the 1956 series, five of the 14 did not live (37%). Both series show what a high perinatal mortality there is among babies born before 37 weeks. The measures taken have reduced the incidence of prematurity; and this has been a factor in the reduction of perinatal mortality. Success in prolonging the pregnancies in cases in which proteinuria does not occur has been accompanied by an increase in the number of inductions of labour required after 37 weeks with no fœtal loss.

Fœtal Prognosis.

In the 1946-1947 series, the perinatal mortality rate was 11% and in 1956 the uncorrected perinatal mortality rate was 8%. However, the perinatal mortality for 1956 was complicated by the presence of three congenital abnormalities, and if we do not count these in the figures we have a corrected perinatal mortality rate of 5%. This is not a statistically significant reduction when compared with 11% in the 1946-1947 series. In 1957, the perinatal mortality among 116 patients with high blood pressure was two.

When the 1956 and 1957 series are combined and the initial diastolic blood pressures are taken into account, there is a significant decrease in the perinatal mortality when compared with the 1946-1947 series.

To sum up, there has been a reduction in the perinatal mortality in the series under discussion as compared with that found ten years ago. When the diastolic blood pressure was kept below 90 mm. of mercury during pregnancy, the fœtal wastage was nil. Thus it would seem that the aim of therapy is to ensure that the blood pressure be kept below 90 mm. of mercury; if it can be, a successful pregnancy can be expected.

If we combine the experience of the 1956 and the 1946-1947 series, there are 18 patients in Group III who started pregnancy with a diastolic blood pressure of 110 mm. of mercury or more and were allowed to continue with the pregnancy. Sixteen of these patients took home a live and

TABLE XIV.
Period of Gestation when Delivered—1946-1947 Series.[1]

Initial Diastolic Blood Pressure in Millimetres of Mercury.	Pre-viable.	Weeks.															Total.
		28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	
90 to 99	—	2 (1)	—	—	—	1 (1)	—	—	—	5 (0)	2 (0)	10 (0)	9 (0)	18 (2)	1 (0)	8 (0)	56 (4)
100 to 109	2 (2)	1 (1)	—	—	—	—	—	2 (0)	1 (0)	2 (0)	2 (0)	6 (2)	1 (0)	5 (0)	4 (0)	—	26 (5)
110 or more	—	—	—	—	—	2 (0)	1 (0)	—	1 (0)	1 (0)	1 (0)	2 (1)	—	2 (0)	1 (0)	1 (0)	12 (1)
Total ..	2 (2)	3 (2)	—	—	—	3 (1)	1 (0)	2 (0)	2 (0)	8 (0)	5 (0)	18 (3)	10 (0)	25 (2)	6 (0)	9 (0)	94 (10)

[1] Figures in parentheses refer to perinatal mortality.

healthy baby. From the figures presented, therapeutic abortion should not be carried out for fœtal reasons.

No attempt has been made to determine whether any one of the changes in treatment could be singled out as being the major factor in producing the improvement seen on comparing the 1956 series with the 1946-1947 series. The important differences in treatment are regular antenatal visits, control of weight gain by the use of a reduction diet with a high protein content, restriction of sodium intake, immediate admission to hospital for rest if required; and the use of hypotensive drugs. Townsend (1959) discusses other factors which may have influenced the improvement.

CONCLUSIONS.

1. When the method of treatment outlined for the 1956 series is used, high blood pressure and pregnancy are not dangerous to the mother. Therapeutic abortion is justifiable only in the presence of malignant hypertension; this occurs rarely.

2. The 1956 regime has significantly reduced the perinatal mortality rate to a figure of 5% or lower. There is no fœtal indication for therapeutic abortion.

3. Hypotensive drugs and bed rest are effective in reducing the diastolic blood pressure during pregnancy.

4. It should be the aim of treatment to reduce the diastolic blood pressure below 90 mm. of mercury. If this is achieved, the perinatal mortality will be very small.

5. The occurrence of a mid-pregnancy drop in blood pressure is a favourable sign for the fœtus and an indication of a lessened risk of development of proteinuria in the mother.

6. The initial diastolic blood pressure is a more reliable index to the prognosis for the fœtus than is the initial systolic blood pressure.

7. It is the rise or fall in the blood pressure that is important. It is impossible and unnecessary to lay down a normal level of blood pressure for pregnant women.

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GAS GANGRENE AFTER THE INJECTION OF ADRENALINE-IN-OIL, WITH A REPORT OF THREE CASES.

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GAS GANGRENE developing after a therapeutic injection of adrenaline-in-oil is a spectacular catastrophe with important medical and medico-legal implications. A search of the literature reveals relatively few reported cases. Several series of cases of gas gangrene due to the injection of a variety of substances, of which adrenaline was the commonest, have been described by Continental authors. However, there seem to have been only two previous cases described from British sources.

Our attention was drawn to the matter when two patients, one of whom died, presented within a few weeks of each other with gas gangrene developing after the injection of adrenaline-in-oil. We have since learned of a third patient, who died some years ago from the same cause.

Reports of Cases.

CASE I.—Mr. A., aged 48 years, a grazier, was given an injection of 1 ml. of adrenaline-in-oil into the right deltoid muscle for an attack of asthma at 8 p.m. on October 10, 1940. The arm became painful and swollen at about 11 a.m. on the following day, and he was admitted to hospital, where he was first examined at 5.15 p.m. on October 11. There was extensive cellulitis of the right arm, with marked redness and swelling over the site of injection. The temperature was 99·5° F., and the pulse rate was 108 per minute. He was given an injection of 15 mg. of morphine for severe pain, and treatment with sulphonamides was commenced. At 11.15 p.m. the pain was still severe, and the swelling had extended on to the chest wall below the clavicle. Crepitus was not present. He had a fair night's sleep, but suddenly collapsed at 6.15 a.m. on the morning of October 12. The temperature was 99·5° F., the pulse rate was 108 per minute, and the blood pressure was 80/60 mm. of mercury. There was dusky discoloration of the skin, and two small vesicles on the inner aspect of the arm had developed, which were discharging red-brown fluid. Crepitus was still not palpable. Polyvalent gas-gangrene antiserum was administered. At 8 a.m. he complained of abdominal pain; the pulse rate was 144 per minute and the pulse was difficult to feel. He had passed only 15 ml. of urine since his admission to hospital, and became moribund at 8.15 a.m. Death occurred at 9.45 a.m. on October 12, about 38 hours after the initial injection of adrenaline-in-oil.

At autopsy there was gas gangrene of the muscles of the right arm and pectoral region, and gas was present in the liver and spleen, the latter being enlarged. The left ventricle was slightly enlarged and the lungs were emphysematous.

Clostridium welchii was isolated from the necrotic muscles and from the spleen. Cultures of other ampoules of adrenaline-in-oil from the same box, and cultures from the syringe and needle used for the injection failed to grow the organism. The syringe and needle had been kept in methylated spirit.

CASE II.—Mr. B., aged 43 years, a truck driver, developed an urticarial rash, for which he received an injection of 1 ml. of adrenaline-in-oil into the right buttock at 9 p.m. on March 17, 1959. Next morning the buttock had become painful and swollen, and he was given an injection of procaine penicillin that evening. Swelling and pain persisted, and on the following morning (March 19) the swelling had extended to the right leg and crepitus was noted.

He was admitted to hospital on March 19, with the diagnosis of gas gangrene. At this stage he was alert, the temperature was 100° F., the pulse rate was 120 per minute and the blood pressure was 130/80 mm. of mercury. The right buttock was very swollen around the injection site, with bluish discoloration of the skin, and surrounding tense œdema. Subcutaneous emphysema extended from the buttock downwards over the entire right leg and upwards over the iliac crest into the flank. The urine was red in colour.

Treatment was begun with high dosage of crystalline penicillin given intramuscularly, and 40,000 units of gas-gangrene antiserum were given in divided doses intramuscularly over a period of six hours. Aspiration of the buttock yielded a small amount of thin, blood-stained fluid. A smear showed Gram-positive bacilli, and on culture *Cl. welchii* Group A was grown. Blood culture yielded no growth of pathogens. His general condition remained good for several hours, but overnight it deteriorated suddenly with the development of peripheral circulatory failure. His systolic blood pressure was 75 mm. of mercury, and his extremities were blue and cold. Serum and saline were administered intravenously, and a further 60,000 units of gas-gangrene antiserum were given, half by the intravenous route and half intramuscularly. After five hours his blood pressure had returned to normal and his general condition was much improved. He passed 600 ml. of urine on March 19, but thereafter his urinary output fell below

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500 ml. per day for four days. Over this period his condition deteriorated, with mental confusion, hiccup and a rising blood urea level. There had been little change in the swelling of the buttock other than the development of central fluctuation. The hæmoglobin value had fallen from 15 grammes per 100 ml. on March 19 to 12·2 grammes per 100 ml. on March 24, despite the transfusion of 1000 ml. of blood. He was transferred to the Alfred Hospital on March 24 for consideration of dialysis with the artificial kidney.

At this stage he was mentally confused, with persistent hiccup. The jugular venous pressure was elevated by 7 cm. The heart was enlarged, a harsh pericardial friction rub was present, and there were râles at the base of each lung. The liver was enlarged, soft and tender, and the sclera were icteric. There was marked swelling of the right leg and buttock, and an extensive area of cellulitis around the needle-puncture mark with central fluctuation. Surgical emphysema was present as previously outlined. The serum potassium level was 7·2 mEq/l. and the blood urea level 260 mg. per 100 ml. The serum bilirubin content was 2·0 mg. per 100 ml., and the cephalin flocculation test produced a strongly positive result.

Operation was performed on March 25. Incision into the fluctuant area of the right buttock exposed necrotic, liquefying, subcutaneous fat, with underlying necrosis of the

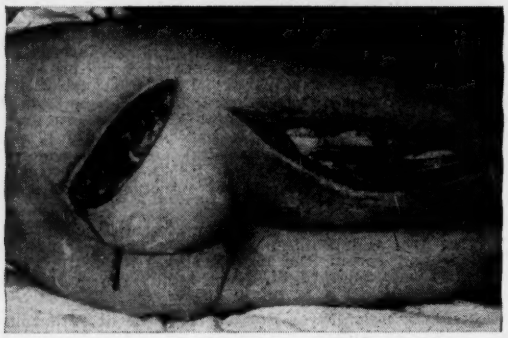

FIGURE I.

Gas gangrene of the buttock after the injection of adrenaline-in-oil. Mr. B., aged 43 years. Photograph showing the appearance of the wounds after the initial operative *débridement*.

gluteus maximus muscle. A wide excision of skin and subcutaneous fat was performed, with drainage of a quantity of brownish pus. The necrotic superficial part of the gluteus maximus was excised. A second longitudinal incision was made lower in the thigh, and further necrotic, gas-distended fat was excised, together with the necrotic superficial portion of vastus lateralis (Figure I). Both wounds were lightly packed.

Diuresis began the following day, and his urinary output over the succeeding days was between 1500 and 2000 ml. The blood urea level continued to rise for a period and reached a maximum of 360 mg. per 100 ml. on March 26.

The cellulitis of the buttock continued to extend and he remained febrile, so a further exploration of the wound was performed on March 29. The buttock wound was enlarged, and a further excision of offensive and obviously gangrenous muscle was performed. Almost the entire gluteus maximus was sacrificed down to the ilium. He received a transfusion of 900 ml. of blood during the operation.

After this his general condition commenced to improve rapidly and the blood urea level fell steadily. The wounds granulated slowly, and secondary suture of the wound in the thigh was later performed. He was discharged from hospital on May 8, 1959, when the wound of the buttock had almost healed. When he was seen in the out-patient department on October 10 both wounds were soundly healed with relatively little deformity (Figure II), and he had returned to work as a truck driver. Apart from occasional stiffness and pain in the right hip, he felt well. The blood urea level was 35 mg. per 100 ml., and examination of the urine showed no abnormality.

Gram staining of the fluid from the buttock before therapy was instituted revealed Gram-positive bacilli, and culture produced a growth of *Cl. welchii* Group A. Culture of pus and necrotic muscle after penicillin therapy grew a few coliform bacilli only. Examination of sections of the muscle revealed marked necrosis and autolysis, with only slight inflammatory reaction. Culture of the syringe and needle used for the injection failed to grow the organism, but *Proteus vulgaris* was cultured from the syringe.

CASE III.—Mr. C., aged 52 years, a potato inspector, had suffered from asthma for three years and had often been relieved in attacks by the intramuscular injection of adrenaline-in-oil. He was examined by his doctor at 10 a.m. on May 20, 1959, for an asthmatic attack associated with a mild respiratory infection, the temperature being 101° F.

FIGURE II.

Gas gangrene of the buttock after the injection of adrenaline-in-oil. Mr. B., aged 43 years. Photograph showing the final appearance seven months later.

He was given an injection of 1 ml. of adrenaline-in-oil into the left buttock, and a course of chloramphenicol was begun. The same evening he complained of severe pain at the injection site and notified the doctor. When he was examined at 1.30 a.m. on May 21 the temperature was 100° F. and the pulse rate was 108 per minute. The left buttock was swollen and red, and surgical emphysema was apparent.

He was immediately transferred 83 miles to Melbourne, where he was first seen in the casualty department at 4.50 a.m. The mass in the buttock was aspirated, and a small amount of foul-smelling gas and fluid was obtained. Gram staining of the fluid demonstrated vast numbers of Gram-positive rods with thin capsules and subterminal spores.

He was admitted to hospital. Further examination in the ward showed him to be an apprehensive, alert, wheezing, middle-aged man. The temperature was 101·6° F., the pulse rate was 120 per minute, and the blood pressure was 160/90 mm. of mercury. In his chest generalized expiratory

rhonchi were audible. The left buttock was obviously enlarged and very tender. A mass, measuring 13 by 8 cm., was palpable in the centre of the buttock surrounding a puncture mark. An intravenous infusion of normal saline was commenced, and 2,000,000 units of crystalline penicillin were given intravenously.

At 8.45 a.m. he appeared very much more restless, and the sclera were definitely icteric. The buttock had increased further in size, and a large area of blue discoloration could be seen extending from the buttock up towards the back. Blood taken for grouping and cross-matching was found to have hæmolysed before it could be used. A further dose of 2,000,000 units of penicillin was given intravenously. Blood taken at this stage revealed the whole blood hæmoglobin value to be 12·1 grammes per 100 ml., with a serum hæmoglobin value of 4·7 grammes per 100 ml. Thus the total effective hæmoglobin was only 7·4 grammes per 100 ml., and rapid hæmolysis was occurring. "Periston N" (polyvinylpyrrolidone, 500 ml.) was given rapidly immediately prior to induction of anæsthesia, and a further 500 ml. were given during and following induction, in an endeavour to adsorb *Cl. welchii* toxin. The pre-induction systolic blood pressure was 130 mm. of mercury, and the pulse rate was 130 per minute. The post-induction blood pressure was 120 mm. of mercury; this fell to 70 mm. during the operation, but rose with the administration of blood and remained between 70 and 90 mm.

A wide excision of skin was performed, and necrotic, black, offensive muscle was excised. The tissues were extremely friable, and the muscles found to be involved were the gluteus maximus, medius and minimus, pyriformis, and portion of sacro-spinalis and the erectores spinæ. These were excised down to the greater sciatic notch, with exposure of the sciatic nerve. The wound was irrigated several times with hydrogen peroxide solution (30 volumes *per centum*), packed lightly, and surrounded by three counter-incisions, through which corrugated rubber drains were inserted. Throughout the operation 3·5 litres of blood were administered. At the conclusion of the operation at 1·45 p.m. further blood examinations were performed; these revealed a whole blood hæmoglobin value of 11·0 grammes per 100 ml. and a serum hæmoglobin value of 3·5 grammes per 100 ml. Hence, after 3·5 litres of blood, his effective hæmoglobin value was still only 7·5 grammes per 100 ml.

In view of the gross hæmolysis still occurring an exchange transfusion was arranged for 2.30 p.m. However, in the intervening half hour the patient became very much more restless, and pulled the intravenous cannula out. His jaundice appeared to increase, and although the cannula was reinserted and blood was administered rapidly, he died at 2.40 p.m. as the exchange transfusion apparatus was being wheeled into the ward. He remained acutely alert until death, which occurred 29 hours after the original adrenaline-in-oil injection and 17 hours after the onset of symptoms.

The syringe used for the injection had been kept in "Zephiran" (1: 1000 solution). Cultures of the "Zephiran" solution, syringe and needle, and of other ampoules of adrenaline-in-oil from the same box failed to yield *Cl. welchii*. At autopsy, there was a large operative wound of the left buttock, the margins of the wound consisting of healthy muscle. The heart was enlarged and showed marked coronary sclerosis, the lungs showed emphysema, and a tracheitis was present. The kidneys and spleen were black in colour.

Discussion.

Cooper (1946) reported the first case in Britain of gas gangrene occurring after a hypodermic injection of aqueous adrenaline solution into the arm.

Various Continental authors had previously described cases of gas gangrene occurring after a variety of therapeutic injections (of which adrenaline was the most common), with a very high mortality rate. Although earlier reports had stressed the likelihood of endogenous infection, Cooper considered that exogenous sources were more probable.

Tonge (1957) reported the first example in Australian writings of gas gangrene after the injection of adrenaline-in-oil. The patient was a young girl, and death occurred within 48 hours of an injection of adrenaline-in-oil into the thigh. He reviewed the literature and made pertinent observations on methods of syringe sterilization. Infection was considered to be almost certainly exogenous.

Adrenaline differs from other substances, such as phenol and calcium chloride, in its ability to render tissues more susceptible to *Cl. welchii* infection, in that adrenaline in the doses used does not cause tissue necrosis. The vasoconstrictor effect of adrenaline, by causing local ischæmia and inhibition of the normal inflammatory reaction, appears to allow bacterial multiplication to continue unchecked (Evans, Miles and Niven, 1948). By the time when the local effect of adrenaline has disappeared, sufficient growth may have occurred for clinical infection to develop.

Clinically, gas gangrene may take the form of localized clostridial cellulitis (the mildest type), localized clostridial myositis, or diffuse myositis with toxæmia. In Cases I and III toxæmia was a feature, while Case II exemplified localized myositis of severe degree, responding to treatment with antibiotics, antiserum and surgery.

Renal failure is likely to occur in severe cases of gas gangrene, owing to a combination of hæmolysis (which was particularly marked in Case III) and renal ischæmia following peripheral circulatory failure, and will contribute to the mortality and morbidity. The prophylaxis of renal failure by avoidance of hypotension in the initial stages is important.

Clinically, the development of gas gangrene after a therapeutic injection of adrenaline is characterized by severe symptoms which cause medical opinion to be sought early. Because of the importance of early treatment in influencing prognosis in this condition, doctors should be aware of the increased likelihood of clostridial infection after the injection of adrenaline. In the cases here described, and in those previously reported (Cooper, 1946; Tonge, 1957), symptoms of local pain, swelling and redness of the skin occurred within a few hours of injection. The signs of marked cellulitis in the neighbourhood of the injection site, together with a severe systemic reaction, may point to the diagnosis, especially if surgical emphysema is present. However, crepitus need not be an invariable feature, despite overwhelming toxæmia, as seen in Case I. Mental alertness, despite an obviously grave illness, may be a striking feature, and may persist, as in Case III, until just prior to death.

In each of the three cases described, and in the one reported by Tonge (1957), the progress of the disease shows the following two phases:

1. Onset of symptoms. There is an initial period of early development of symptoms of pain, local reaction and a general toxæmic response of variable degree, but without circulatory failure and with a normal blood pressure.

2. Circulatory failure. After a period of several hours from the onset of symptoms, decompensation occurs, with the development of peripheral circulatory failure and marked hypotension, probably associated with severe hæmolysis and continuing toxæmia. Death occurred early in this stage of circulatory failure in the fatal cases, and if this stage is survived, renal failure may be a sequel (Case II). Treatment should thus be directed towards anticipating and preventing the stage of circulatory failure, and it is possible that more vigorous resuscitation in the early period with a plasma expander such as blood or plasma would be desirable, despite a normal blood pressure.

The course of the disease is very rapid, symptoms appearing within a few hours of injection, and circulatory collapse and death after a short period (38 hours and 29 hours respectively in Cases I and III). Early diagnosis is thus of paramount importance, and may be achieved by examination of smears and culture of fluid aspirated from the site of maximum swelling (Cases II and III). If organisms morphologically resembling *Cl. welchii* are found, treatment should be vigorous, and rapid transfusion of blood or plasma, the administration of penicillin and early surgical drainage are recommended. Gas-gangrene antiserum should be given intravenously without awaiting confirmation of the diagnosis from culture.

The source of infection with the organism is of interest, and in the cases described it is considered to be almost certainly exogenous. Exogenous infection may be by several vectors, as follows: (1) contamination of the

syringe, needle or injected solution by vegetative organisms or spores, with direct inoculation into the tissues; (ii) organisms resident on the skin at the injection site being carried into the tissues by the needle, as a result of imperfect sterilization of the skin. Clostridia are widely distributed, and contamination of syringe or needle may readily occur. Sterilization of instruments by chemical means or by boiling for less than ten minutes (Wilson and Miles, 1955) is no guarantee of destruction of spores. However, in none of these cases was *Cl. welchii* subsequently cultured from the syringe or needle, although *Proteus vulgaris* was cultured on one occasion (Case II).

With regard to resident skin organisms, *Cl. welchii* is said to be uniformly present in human fæces (Wilson and Miles, 1955), and contamination of the skin of the buttock is highly likely. Cultures taken from unprepared abdominal skin before elective surgery have shown clostridia to be present in 21·7% of cases (Roberts, Johnson and Bruckner, 1933). It is of some interest perhaps, in view of the wide distribution of *Cl. welchii* in the soil, that one patient was a grazier and another a potato inspector.

There is no method of sterilization of the skin which can be guaranteed to destroy spores. Perhaps the best compromise between bactericidal efficiency and harmlessness to the skin is the use of chlorhexidine ("Hibitane", Annotation, 1958), and a solution of 0·5% to 1% chlorhexidine in alcohol (70%) is recommended as the most suitable skin antiseptic.

It may seem reasonable to administer adrenaline or adrenaline-in-oil by injection into the arm rather than the buttock; but although contamination at this site should perhaps be less likely, infection may still occur (Case I; and Cooper, 1946).

In practice, it is apparent that care in sterilization of syringe, needle and injection site is vital, particularly in relation to the special hazard of gas-gangrene infection after injections of adrenaline in aqueous or oily solution, and the recommendation of a domestic pressure cooker (Tonge, 1957) as a quick and effective sterilizer has much to commend it.

It should be possible to guarantee sterility of instruments and of the solution injected; but there is no way of destroying spores of *Cl. welchii* on the skin prior to injection, although vegetative organisms will be rapidly eliminated by the antiseptic recommended.

It has been suggested (Tonge, 1957) that adrenaline-in-oil may be more effective than aqueous adrenaline solution in enhancing clostridial infection because of its more prolonged vasoconstrictive action. However, recent experiments have shown no difference between the effect of adrenaline in aqueous and in oily solution (Bishop and Marshall, 1960).

Aqueous adrenaline solution is usually administered by subcutaneous injection into the arm; but adrenaline-in-oil must be administered intramuscularly, and the consequence of infection by *Cl. welchii* is far more serious in muscle (clostridial myositis) than in subcutaneous tissue (clostridial cellulitis). The complication of gas gangrene developing after an intramuscular injection of adrenaline-in-oil is admittedly an uncommon one; but should it occur, the mortality and morbidity are very great.

In view of these facts, for our part, we consider the intramuscular use of adrenaline-in-oil to be an unjustifiable risk.

Summary.

Three cases of gas gangrene developing after the intramuscular injection of adrenaline-in-oil are described, with clinical and bacteriological findings. One injection was into the arm, and two were into the buttock. Two of the patients died, and one developed renal failure, but survived.

The cases showed similar clinical features. A stage of early onset of symptoms developed within a few hours of injection with a marked local reaction and symptoms of toxæmia, and during this period the blood pressure was normal. A second stage of sudden circulatory collapse with marked hypotension followed, and hæmolysis was a feature. Renal failure was a sequel in the patient who survived this stage. Death in the fatal cases occurred within 40 hours of the initial injection.

Adrenaline in oily or aqueous solution is seen to enhance markedly infection with *Cl. welchii*, and this fact should be more widely known. The possible sources of infection in these patients are discussed, and are considered to be exogenous.

In view of the potential dangers of adrenaline in oily or aqueous solution, strict care is advised in the sterilization of syringe, needle and injection site when adrenaline is administered, and oily solutions are to be avoided.

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THE ENHANCEMENT OF CLOSTRIDIUM WELCHII INFECTION BY ADRENALINE-IN-OIL.

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THE injection of aqueous adrenaline solution together with a bacterial suspension of *Clostridium welchii* has been shown to enhance the infectivity of the organism in the guinea-pig (Cooper, 1946). This is probably due to transient vasoconstriction at the site of injection (Evans, Miles and Niven, 1948). It has since been suggested that the use of adrenaline-in-oil as a vehicle may further enhance infection by *Cl. welchii* because of its prolonged vasoconstrictive effect (Tonge, 1957). This suggestion is interesting in view of recent reports of gas gangrene in man following the therapeutic use of an intramuscular injection of adrenaline-in-oil (Tonge, 1957; Marshall and Sims, 1960).

It was decided to study the effect of adrenaline-in-oil in potentiating *Cl. welchii* infection in the guinea-pig and to compare the result with the effect of aqueous adrenaline solution.

Methods.

The strain of *Cl. welchii* used in these experiments was isolated from a patient with gas gangrene occurring after an intramuscular injection of adrenaline-in-oil into the buttock. The growth from an eighteen-hour anaerobic culture on meat infusion agar was washed off in sterile Ringer's solution, centrifuged and washed three times. Tenfold dilutions of the final suspension were prepared in sterile Ringer's solution, and a viable count was made by the technique of Miles and Misra (1938).

The guinea-pigs used each weighed between 300 and 400 grammes, and injections were given intramuscularly into the hind leg. In preliminary experiments to determine the doses of adrenaline-in-oil and of aqueous adrenaline solution which would be tolerated, it was found that adrenaline-in-oil (500 μg. in 0·25 ml.) and aqueous adrenaline solution 1:8000 (125 μg. in 0·9 ml.) had no detrimental local or general effects when injected alone. However, it was found that with a higher concentration of aqueous adrenaline solution—for example, 0·5 ml. of 1:1000 adrenaline (500 μg.), general reactions sometimes occurred, consisting of twitching, epistaxis and tachycardia, and occasionally death within a few minutes. These reactions did not occur with a similiar dose of the longer acting adrenaline-in-oil. Groups of three guinea-pigs were injected with 0·1 ml. of a series of tenfold dilutions of *Cl. welchii* suspension, together with one of the following sterile solutions: (*a*) 0·25 ml. of Ringer's solution; (*b*) 0·25 ml. of arachis oil; (*c*) 0·25 ml. of adrenaline in arachis oil (500 μg. of adrenaline); (*d*) 0·9 ml. of aqueous adrenaline solution 1:8000 (125 μg. of adrenaline).

Control groups of three guinea-pigs were injected with (*b*), (*c*) and (*d*) alone. A further group of three guinea-pigs received 0·1 ml. of the supernatant fluid from the most concentrated suspension of *Cl. welchii*, in order to ensure that no preformed toxin was present.

All guinea-pigs were observed for five days. Deaths were recorded as due to gas gangrene only when a typical local lesion was found at autopsy and examination of a smear from the exudate showed numerous Gram-positive bacilli morphologically resembling *Cl. welchii*.

Results.

The results are recorded in Table I. It is seen that the minimum lethal dose of the strain of *Cl. welchii* used lay between 5×10^7 and 5×10^8 organisms. The minimum lethal dose was lowered one thousandfold to lie between 5×10^4 and 5×10^5 when adrenaline-in-oil (500 μg.) or aqueous adrenaline solution 1:8000 (125 μg.), was injected together with the bacterial suspension. Oil by itself did not alter the minimum lethal dose of the bacteria.

TABLE I.

The Effect of Oil, Adrenaline-in-Oil, and Aqueous Adrenaline Solution on the Minimum Lethal Dose of Clostridium Welchii.

Dose of *Cl. welchii*. (Number of Organisms.)	Deaths from Gas Gangrene.[1]			
	Organisms Plus Ringer's Solution.	Organisms Plus Oil.	Organisms Plus Adrenaline-in-Oil.	Organisms Plus Aqueous Adrenaline Solution.
5×10^8	3/3	3/3	3/3	3/3
5×10^7	0/3	0/3	3/3	3/3
5×10^6	0/3	0/3	3/3	3/3
5×10^5	0/3	0/3	3/3	3/3
5×10^4	0/3	0/3	0/3	1/3
5×10^3	0/3	0/3	0/3	0/3

[1] 1/3=of three guinea-pigs injected, one died from gas gangrene.

Discussion.

The results of this investigation confirm the findings of previous workers that adrenaline enhances infection by *Cl. welchii* in the guinea-pig (Cooper, 1946; Evans *et alii*, 1948). The results have also shown that adrenaline-in-oil is no more effective in enhancing *Cl. welchii* infection in the guinea-pig than is aqueous adrenaline solution. In fact, as the minimum lethal dose of *Cl. welchii* was lowered one-thousandfold by both, despite a larger dose of adrenaline-in-oil (500 μg. as opposed to 125 μg.), the latter is possibly less effective than aqueous adrenaline solution.

The results are somewhat surprising, as the mode of action of adrenaline in enhancing infection is thought to be a transient local vasoconstriction (Evans *et alii*, 1948). Tonge (1957) suggested that the more prolonged effect of adrenaline-in-oil might produce an environment even more favourable for bacterial multiplication, but this has not been confirmed by these results.

A possible explanation of the results may be that enhancement of infection requires only initial vasoconstriction at the injection site, which could be produced by a very small local concentration of adrenaline. Cooper (1946) found that aqueous adrenaline solution was capable of enhancing infection in a dilution of 1 in 128,000. Once bacterial multiplication begins as a result of this vasoconstriction, continued multiplication would rapidly maintain local conditions suitable for further growth, and the further slow release of adrenaline from the oily solution would be unnecessary.

The observation that oil at the site of injection has no effect on the infectivity of *Cl. welchii* is reassuring, when the use of sclerosants in oily solution for the treatment of hæmorrhoids is considered. *Cl. welchii* is normally present in human fæces, and the complete sterilization of bowel mucosa before injection would be difficult to achieve if there was evidence that it was necessary.

These experiments serve to underline the necessity for care in sterilization of instruments and injection site when adrenaline in aqueous or oily solution is being used.

Summary.

A series of experiments was performed to determine whether adrenaline in oily solution was more effective than aqueous adrenaline solution in enhancing infection with *Cl. welchii* in the guinea-pig.

Infection with *Cl. welchii* was found to be enhanced one-thousandfold by adrenaline in aqueous or oily solution, but no significant differences existed between the effects of the two.

Oil alone had no effect on infectivity.

In view of the potential dangers of adrenaline in oily or aqueous solution, strict care in sterilization of instruments and injection site is urged.

Acknowledgements.

We are grateful to Professor M. R. Ewing and Dr. Nancy Hayward for their help in the preparation of this paper.

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BODY TEMPERATURE AND HOLOENDEMIC MALARIA IN NEW GUINEA.

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A FULL account of the epidemiology of malaria in the Maprik area of the Sepik District of the Territory of Papua and New Guinea was given by Peters and Standfast (1960). It was shown that the intense transmission there results in a picture of holoendemicity as defined by Metselaar and Van Thiel (1959), and even as defined by the World Health Organization (1951). It is generally recognized that in areas of holoendemic malaria the degree of premunity is such that maximum parasite densities

are reached by the age of about three years, and parasite rates fall in children aged about five years and over. The tolerance of infants to a high parasite load is well known; but to what degree this is a true premunity and to what degree the infants' defence mechanisms are enhanced by maternal factors or diet are still ill defined. It is usually assumed that malaria is responsible for a high infant mortality in areas where *Plasmodium falciparum* is present and its transmission is intense.

In the Maprik area it has been shown that up to 60% of babies die before attaining the age of about 18 months. To what degree malaria does in fact contribute to this high mortality is a matter of speculation, which can be resolved adequately only when malaria has been eradicated from such an area. Information is gradually appearing at Maprik, where a residual spray campaign is rapidly freeing the region of malaria transmission, that there are a number of unrecognized diseases responsible for infant morbidity in a population from which malaria parasitæmia is disappearing (Schofield, personal communication).

Method.

In September, 1957, the preoperative malaria survey was made in the Maprik Pilot Project area. In four villages (Bobmagum, Chigiangu, Tendegum and Tugaikum II of the North Wosera census division), axillary temperatures were recorded of 611 people of all ages. Standard clinical thermometers were held in the axilla for three minutes and then read by the writer. A thick blood film was taken from each individual after his temperature had been recorded, and the films were later examined by the writer at the base laboratory in Maprik.

Best and Taylor (1955) quote 98·6° F. as the normal body temperature taken by mouth and 98·1° F. as the normal axillary temperature. (In the rest of this paper all temperatures quoted are in degrees Fahrenheit.) They state that the normal temperature may vary between 0·5° and 1·0° at different times of the day, and that strenuous exercise may also cause a temporary rise of 1° or even up to 4°. Spontaneous variations may occur up to 1° or 2° during the first year of life, and in older children emotional stress may produce a similar transitory rise. For the purpose of this survey it was decided to select 98·4° F. as the normal axillary temperature. Temperatures were recorded to 0·1°, but were grouped into intervals of 1·0° for statistical analysis. The individual record cards were marked to show the elevation of temperature above 98·4°, so that temperatures of 98·4° or below were classed as "0".

The numbers of natives in each age group were as follows: under 2 years, 59; 2 to 4 years, 66; 5 to 14 years, 170; 15 to 19 years, 86; over 20 years, 230. The examinations were made at two central points at which the villagers congregated. This necessitated a walk of several miles in the morning sun for most people. The survey was made between 10.30 and 17.30 hours; but owing to the small numbers involved it was decided not to analyse separately the records of people seen at different times. Single-dose "Chloroquine" therapy was given to all those examined whose temperature was above 99·4°.

Frequency Distribution of Body Temperature.

No significant sex differences were found. The following distribution was found for the whole group of 611 examinees: 98·4° or less, 40·8%; 98·5° to 99·4°, 42·1%; 99·5° to 100·4°, 12·8%; 100·5° to 101·4°, 2·0%; 101·5° to 102·4°, 1·0%; 102·5° to 103·4°, 1·1%; 103·5° to 104·5°, 0·2%. If the groups are further analysed by age groups, the pattern shown in Table I appears.

It was mentioned above that the majority of these people were examined in the middle of the day after they had walked for several miles in the sun. It is certain that most of the toddlers and all the infants were carried by their parents. This probably explains why 79·3% of the five to 19 years age group and 92·7% of the adults had temperatures ranging up to 99·4°, while the pattern of temperatures in infants and toddlers shows a continuous decline in frequency after 98·4°. For the purpose of the present discussion it seems reasonable to assume that pyrexia in children of four years and under should be defined as any recording in excess of 98·4°, while in the older age groups up to 99·4° should be considered within the normal limits under these circumstances. Colbourne (1955) considered that an oral temperature of 99° to 99·4° was normal in West African school-children. On this basis, 57·6% of children aged under five years, 20·7% of the five to 19 years age group and only 7·3% of adults showed some measure of pyrexia. Temperatures over 101·4° were found in 7·2% of children aged under five years, in 2·3% of the five to 19 years age group, and in no adults. This figure of 7·2% is made up of 11·9% of 59 babies aged under two years and 3·0% of 66 toddlers aged two to four years.

Table I.

Frequency Distribution of Body Temperature in Different Age Groups.

Temperature. (Degrees Fahrenheit.)		Age Group and Frequency (*per Centum*).		
Range.	Mean.	Under 5 Years. (125)	5 to 19 Years. (256)	Over 19 Years. (230)
Below 98·5		42·4	35·5	45·9
98·5– 99·4	99	29·6	43·8	46·8
99·5–100·4	100	14·4	17·6	6·5
100·5–101·4	101	6·4	0·8	0·8
101·5–102·4	102	4·0	0·35	0
102·5–103·4	103	2·4	1·6	0
103·5–104·4	104	0·8	0·35	0

It is thus seen that there is an apparent decrease in the frequency of pyrexia with increasing age, together with a decrease in the degree of fever, children aged under five years having the highest frequency (57·6%). It should be noted, however, that the survey did not necessarily include the entire populations of the particular villages. It is always possible that a number of the residents who were not seen were ill at home.

Relation of Pyrexia to Parasitæmia.

The thick blood films of 123 children aged under five years were examined for malaria parasites. Of those for whom a normal temperature was recorded, eight films gave negative results and 45 positive. Of those with pyrexia, the films of six gave negative results and of 64 positive results. An examination of these figures by the χ^2 test shows that $P < 0{\cdot}5$—that is, there is no statistically significant difference between the parasite rates of the two groups. It must be emphasized that this statement is based on a single simultaneous examination of blood film and body temperature. It was found that 84·9% of those without pyrexia and 91·4% of those with pyrexia had parasitæmia. Conversely, 8·6% of children with pyrexia were parasite free.

Since parasite densities are usually high enough for parasites to be detected in a single thick film in this age group, it would seem that in this 8·6% of children there was an ætiology other than malaria to account for their pyrexia. At the same time, since we have shown that parasitæmia by no means always results in pyrexia, a proportion of the remaining 91·4% may also have had an alternative cause for their fever.

Parasite Density and Pyrexia.

It was further shown in the small series examined that the parasite density bears no significant relation to the presence or absence of pyrexia (Table II).

An interesting example of the degree of tolerance to parasitæmia in this series is that of an infant, aged two months, with a mixed infection of *P. falciparum* (88,000 parasites per cubic millimetre) and *P. vivax* (50 parasites per cubic millimetre), whose temperature was normal, and

who showed no obvious signs of illness. At the age of two months, it is unlikely that a high degree of premunity has been built up, and in fact this case is strongly suggestive of passive protection acquired from the mother.

Further examples of high degrees of tolerance to a heavy parasite load are the following cases of malaria treated at the Maprik Native Hospital in 1957.

A male patient, aged two years, on admission to hospital had a temperature of 100·8° F.; *P. falciparum* was present in a density of 428,000 per cubic millimetre. He was discharged from the hospital on the fifth day with a normal temperature.

The patient was a female, aged two years. On her admission to hospital her temperature was 101·8° F. There were 186,000 *P. falciparum* parasites per cubic millimetre. She was discharged from the hospital on fourth day with a normal temperature.

TABLE II.

Arithmetic Mean of Parasite Densities per Cubic Millimetre.

Parasite.	Temperature. (Degrees Fahrenheit.)	
	Below 98·5	Above. 98·4
P. falciparum:		
Number of infections ..	20	26
Arithmetic mean	14,450	11,770
P. vivax:		
Number of infections ..	34	43
Arithmetic mean	5050	3510
P. malariæ:		
Number of infections ..	16	35
Arithmetic mean	170	360

The patient was a male aged three months. On his admission to hospital his temperature was 100·2° F. There were 135,000 *P. falciparum* organisms per cubic millimetre. He was discharged from the hospital on the fourth day with a normal temperature.

All these patients were treated with a single intramuscular injection of a suitable anti-malarial drug on their admission to hospital.

Discussion.

Several general conclusions emerge from the data presented above. Firstly, in defining pyrexia, the circumstances under which temperature observations are made must be considered. In adults, prolonged physical exercise and a high environmental temperature and humidity may result in up to 1° F. rise in temperature. The mean midday temperature at Maprik is 87° F. and the relative humidity 75%. Colbourne's (1955) observation on West African school-children is also relevant.

It appears that pyrexia is more frequent in the younger age groups; but it must be remembered that older people who are ill may not attend for examination, and these would obviously influence the results of such surveys as the foregoing. It should also be borne in mind that in any community in a malaria-free area, pyrexia is likely to be encountered most frequently in young children, since it is in childhood that most of the individuals encounter new bacterial and viral challenges against which they build up an active immunity. Furthermore, the temperature response of young children to simple bacterial infections is often far greater than that observed in adults.

A most important observation is that parasitæmia is frequently present in an apparently normal child. This is by no means an original observation; and yet, in all tropical areas where malaria is a common disease, there is a tendency to diagnose (*a*) any patient in whose blood malaria parasites are seen and (*b*) all patients with pyrexia or symptoms of cerebral irritation as suffering primarily from malaria. It cannot be too strongly emphasized that in highly endemic areas malaria is present in a high proportion of the population, especially the infants and children, but that other diseases are also present. It is too easy to assume that an illness is due primarily to malaria, and to omit to look for alternative causative factors. At the same time, it must be admitted that it is frequently very difficult to know whether, for example, the patient is suffering from influenza or from one of the E.C.H.O. virus diseases—which in many cases are self-limiting diseases producing pyrexia of a few days' duration—when he has, at the same time, a fairly high density of malaria parasites. Obviously in such cases it is advisable for a start to treat the malaria.

In the Maprik area, as was stated above, now that a new generation of infants is growing up in the absence of malaria transmission, disease patterns characterized by pyrexia of limited duration are becoming evident (Schofield, personal communication). It is quite possible that such infections explain the splenomegaly noted by Metselaar (1957) in malaria-free infants of the Sentani area of Netherlands New Guinea. Moreover, several cases of encephalitis of unknown ætiology have now been diagnosed at Maprik. These would almost certainly have been attributed a few years ago to cerebral malaria.

Summary.

In the course of the pre-operative malaria survey of the Maprik Malaria Control Pilot Project area, the axillary temperatures of 611 people of all ages were recorded at the time of taking blood samples for malaria parasites.

A rise of up to 1° F. in older children and adults was considered to be the result of exercise rather than true pyrexia. Of children aged under five years 57·6%, of children and adolescents aged five to 19 years 20·7%, and of adults 7·3%, showed some degree of pyrexia.

There was no statistically significant correlation between the parasite rate and the presence or absence of pyrexia in 123 children aged under five years whose blood films were studied.

A high degree of tolerance to heavy parasite densities of *P. falciparum* was noted.

It is emphasized that in a locality where malaria is highly endemic it should not be assumed that malaria alone is responsible for pyrexia. As malaria transmission is interrupted in such an area, other disease patterns become apparent which have been masked previously by malaria.

Acknowledgements.

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PLASMA THERAPY IN HÆMOPHILIA.[1]

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A BETTER UNDERSTANDING of the nature of the hæmostatic defect in hæmophilia has resulted in a more rational approach to therapy. Hæmophilic blood clots imperfectly because it lacks an essential thromboplastin-precursor substance known as antihæmophilic-factor (AHF). The plasma AHF concentration necessary for adequate hæmostasis is probably at least 35% of that found in normal blood (Biggs and Macfarlane, 1957). The aim of therapy in serious bleeding in hæmophilia is to raise the plasma AHF concentration to the hæmostatic range, and to maintain an adequate concentration until bleeding has ceased. Therapeutic agents available for intravenous use are normal fresh human plasma, "fresh-frozen" plasma, or AHF concentrates of human or animal origin (Kekwick and Wolf, 1957; Macfarlane, Biggs and Bidwell, 1954). AHF concentrates are very effective in raising the plasma AHF concentration, but they are difficult to obtain in this country, their administration is often associated with unpleasant reactions, and those of animal origin are antigenic.

Macfarlane *et alii* (1957) described four cases in which successful surgery was performed after the administration of large volumes of fresh or frozen plasma. These authors pointed out the difficulties in obtaining effective plasma AHF levels because of the large volumes of normal plasma required. They preferred to use AHF concentrates of animal origin for major surgical procedures in hæmophiliacs.

In this paper we report our own experiences with fresh or "fresh-frozen" plasma therapy in the management of complications in hæmophilia. We have attempted to assess the danger of circulatory overload when large volumes of plasma are administered, the degree of correction of the coagulation defect possible and the most effective form of laboratory control for this type of therapy. Both mildly and severely hæmophilic subjects were treated for a variety of conditions.

Methods.

Plasma Banking Procedures.

"Fresh-frozen" plasma was prepared by the Western Australian Branch of the Red Cross Blood Transfusion Service. Blood (430 ml. volumes) was collected by gravity in 70 ml. acid citrate-dextrose (ACD) solution. Each bottle was placed in a cool draught for 30 minutes to allow sedimentation of red cells to commence, and then centrifuged in an "M.S.E. Major" refrigerated centrifuge at 1600 r.p.m. for 45 minutes, the temperature being controlled at between 2° and 4° C. The plasma was sucked off into a dry bottle and immediately frozen to −25° C. The whole procedure was completed within two hours of blood collection.

Immediately before use, plasma of the appropriate blood group was completely and rapidly thawed in a water bath at 37° C. with frequent shaking. Plasma was administered through conventional blood-transfusion sets. The bottle was agitated from time to time while the plasma transfusion was in progress. Plasma collected less than three months previously was used for all patients. The plasma obtained from one donation of blood—usually 250 ml.—has been termed a donor unit.

Rate of Plasma Transfusion.

The aim was to achieve a satisfactory plasma AHF concentration as rapidly as possible. In patients being prepared for surgery, an attempt was made to attain this level before the actual surgery commenced. Patients were therefore given a loading transfusion of plasma, usually one litre in one hour or less. Thereafter the rate of transfusion was controlled by the result of laboratory tests, but in those patients subjected to maintenance therapy it was usually one donor unit every four hours. One child in the series received a loading dose of only 400 ml., calculated on the expected blood volume. Whole blood was given as required; this was freshly collected and given at the rate of 500 ml. every four hours. In assessing the results of therapy, 500 ml. of fresh blood has been considered equivalent to one donor unit of plasma.

Laboratory Control of Therapy.

The degree of correction of the hæmostatic defect was assessed by either the thromboplastin screening test (Hicks and Pitney, 1957) or plasma AHF assay (Pitney and Arnold, 1959). In some cases both tests were used. The screening test has the advantage of rapidity, which may be important in deciding the rate of plasma administration. The AHF concentrations of some plasma donor units were also determined.

Reports of Cases.

Nine hæmophiliacs were treated for 12 episodes. The relevant details are summarized in Table I.

CASE I.—A boy, aged 13 years, suffers from moderately severe hæmophilia. His plasma AHF concentration is 2%. He was treated on two occasions. The first plasma transfusion was administered because of an acute hæmarthrosis of the knee causing considerable pain. A transfusion of 750 ml. of "fresh-frozen" plasma was given over a three-hour period. The plasma AHF concentration was 27% at the completion of the transfusion. There was rapid relief of pain and no further increase in joint swelling.

Two months later, he had eight carious teeth extracted under general anæsthesia. A transfusion of 750 ml. of "fresh-frozen" plasma was given during the hour prior to extraction. The plasma AHF concentration increased to 16%. Plasma transfusion was continued at the rate of one donor unit every four hours until a further 750 ml. had been given. The plasma AHF concentration was then 26%. There was no bleeding from the sockets by this time, and therapy was suspended. Bleeding from three sockets commenced on the third day. A further loading dose of 1 litre of plasma was given by transfusion in one hour, followed by fresh blood and plasma for the next 24 hours at the rate of one donor unit every four hours. Bleeding then ceased, the plasma AHF concentration at this time being 31%. Two further loading doses of 1 litre of plasma were given on the sixth and tenth days for the removal of friable clot. After this the sockets healed well, and the patient left hospital 16 days after the tooth extractions.

This patient received a total of 24 donor units of plasma during this episode. Although his plasma AHF concentration reached 31% on one occasion, the result of the thromboplastin screening test remained abnormal throughout therapy.

CASE II.—This boy, aged seven years, suffers from mild hæmophilia. The usual plasma AHF concentration is about 13%. Tonsillectomy was undertaken for chronic tonsillitis with repeated acute exacerbations causing considerable ill-health and retardation of growth. A loading dose of 400 ml. of "fresh-frozen" plasma in one hour raised the plasma AHF level to 50%, and tonsillectomy was performed without incident. Plasma therapy was continued for 28 hours at the rate of one donor unit every four hours. The plasma AHF concentration remained above 30% during this time. Eight hours after the administration of plasma was discontinued, bleeding commenced from both tonsillar fossæ. Three further units of plasma and 500 ml. of blood were given over the next 24 hours. Bleeding ceased soon after the reinstitution of plasma therapy, and he made an uneventful recovery.

He received a total of 13 donor units of plasma. It is probable that maintenance therapy was discontinued too soon after the operation. The bleeding that occurred eight hours later was controlled without difficulty by further plasma.

CASE III.—This patient, aged 30 years, is a moderate hæmophiliac whose plasma AHF concentration is about 6%. He leads an active life and participates in competitive motor-car racing. While pursuing this sport, he

[1] Based on a paper presented to the annual meeting of the College of Pathologists of Australia, Sydney, August, 1959.

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TABLE I.

Case Number.	Age. (Years.)	Indication for Therapy.	Therapeutic Product.	Initial A.H.F. (Percentage.)	Maximal A.H.F. Attained. (Percentage.)	Duration of Therapy.	Total Donor Units Transfused.
I	13	Hæmarthrosis.	Frozen plasma.	2	27	3 hours	3
		Teeth extraction.	Frozen plasma and fresh blood.	2	31	10 days (intermittent)	24
II	7	Tonsillectomy.	Frozen plasma and fresh blood.	13	50	60 hours (intermittent)	13
III	30	Multiple lacerations.	Fresh plasma.	6	23	9 hours	7
			Fresh plasma.	6	29	16 hours.	10
IV	52	Lens extraction.	Frozen plasma.	3	26	50 hours	21
		Enucleation of eye.	Frozen plasma.	3	46	50 hours	20
V	24	Ruptured spleen.	Frozen plasma and fresh blood.	0	50	9 days	52
VI	35	Bleeding tooth socket.	Frozen plasma.	21	46	9 hours.	9
VII	63	Epistaxis.	Frozen plasma and fresh blood.	5	13	24 hours	8
VIII	21	Tooth extraction.	Fresh plasma.	0	7	1 hour	4
IX	15	Teeth extraction.	Frozen plasma.	26	52	7 hours	6

was involved in a collision and received severe lacerations to the scalp, face and buccal mucosa. He was given a total of seven donor units of plasma over a period of nine hours, during which time the lacerations were sutured. Although a plasma AHF level of 23% was attained, there was only partial control of bleeding, and the buccal lacerations continued to ooze. Three days after his admission to hospital he was given a further transfusion of 10 donor units of plasma over a period of 16 hours. Bleeding ceased during this transfusion and did not recur.

CASE IV.—This patient, aged 52 years, is the uncle of the patient referred to in Case I, and is similarly affected with a plasma AHF level of 3%. A traumatic cataract developed after an injury to his eye, and lens extraction was

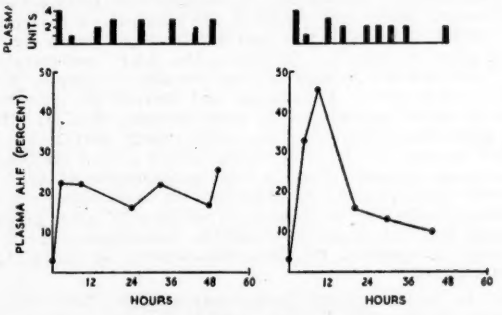

FIGURE I.

Case IV: plasma AHF concentrations during two courses of plasma therapy. The left-hand figure refers to the first treatment for lens extraction and the right-hand figure to the second treatment for eye enucleation. This patient received 21 units of plasma in the first course and 20 units in the second.

carried out under plasma cover. The plasma AHF values during treatment are shown in Figure I. A loading dose of 1 litre of plasma in the hour prior to surgery raised the plasma AHF concentration to 22%. Maintenance therapy was continued for 48 hours after surgery, and the plasma AHF level ranged from 16% to 26%. The result of the thromboplastin screening test became normal. Moderate hyphæma developed after plasma therapy was discontinued.

Three weeks later it was found necessary to enucleate the damaged eye, and plasma therapy was instituted once more. On this occasion, with a similar loading dose the plasma AHF level reached 45%, but maintenance levels were less satisfactory than with the previous transfusion. There was no abnormal bleeding.

CASE V.—This patient, aged 24 years, has been briefly discussed previously (Pitney, 1959). He suffers from severe hæmophilia, and his plasma contains traces only of AHF. He sustained multiple injuries, including a rupture of the spleen, in a motor-car accident. Splenectomy was carried out after intensive preparation with fresh blood and plasma,

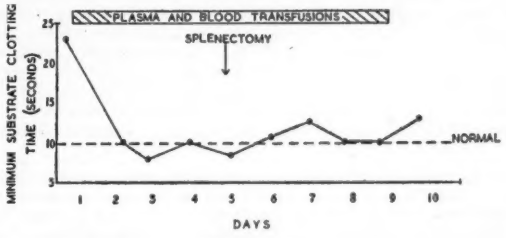

FIGURE II.

Case V: Control of therapy with the thromboplastin screening test. The minimum substrate clotting time in this test, using a normal plasma dilution, is 10 seconds or less.

at a time when the result of the thromboplastin screening test was normal and the plasma AHF concentration 50%. Figure II shows how the thromboplastin screening test was used to control therapy. Plasma transfusion was continued for four days after operation. Apart from a small hæmatoma of the wound, there was no abnormal post-operative bleeding.

CASE VI.—This patient, aged 35 years, suffers from mild hæmophilia with a plasma AHF concentration of about 21%. He was admitted to hospital 24 hours after removal of a tooth because of persistent bleeding from the socket. One litre of "fresh-frozen" plasma was administered in two hours, at the end of which time the plasma AHF value was 46%. He was given a further five units of plasma during the next seven hours. Bleeding ceased during plasma therapy and did not recur.

CASE VII.—This patient, aged 63 years, is the uncle of the patient referred to in Case III, and has a similar plasma AHF concentration of 5%. He was admitted to hospital with epistaxis. He was one of the earlier patients in the series, and at that time we did not appreciate the importance of an adequate loading dose of plasma. He was transfused with fresh blood and frozen plasma at the rate of one donor unit every three hours without a preliminary loading dose. Over a 24-hour period, he received eight donor units of plasma. His plasma AHF concentra-

tion reached a maximum value of only 13%. The epistaxis settled down with morphine and rest, and it is doubtful whether plasma therapy played any part in its control.

CASE VIII.—This patient, aged 21 years, was also treated inadequately early in the series. He is severely hæmophilic, with no demonstrable plasma AHF. Tooth extraction was undertaken after 1 litre of fresh plasma had been given in one hour. This raised the plasma AHF concentration to only 7%. Maintenance therapy was not attempted, and bleeding continued for two weeks, requiring repeated blood transfusions.

CASE IX.—This patient, aged 15 years, suffers from mild hæmophilia and has a plasma AHF concentration of 26%. After the administration of 1 litre of plasma in one hour, two molar teeth were extracted. A further two units of plasma were transfused during the succeeding six hours. The plasma AHF concentration was raised to 52%, and there was no excessive bleeding from the tooth sockets.

Discussion.

It is often difficult to assess the results of therapy in hæmophilia, as a series of patients cannot be considered a uniform group. The plasma AHF concentration is genetically determined, and may range from zero in some patients to levels not much below the lower limit of normal in others. Patients with similar plasma AHF concentrations may differ in their liability to abnormal bleeding. The response shown by the same patient may vary from time to time, depending on whether he is in a "good" or a "bad" phase.

As a general rule, however, patients with appreciable amounts of AHF in the plasma are mildly affected. They have normal whole-blood coagulation times and may be recognized only by the use of sensitive laboratory tests (Pitney, 1957). The hæmostatic defect in such patients is relatively easy to control, and it may be reasonable to carry out surgical procedures on a mildly hæmophilic subject which would not be advisable on a severely affected patient. It is important, therefore, to assess as accurately as possible the likelihood of a particular patient to bleed excessively before any surgical procedures are performed. The history of past hæmorrhagic episodes, especially the occurrence of hæmarthroses, is a useful guide. Patients with prolonged whole-blood coagulation times are usually moderately or severely affected; the plasma AHF assay is, however, the most accurate laboratory method of assessment available at present.

We have employed plasma therapy to arrest hæmorrhage either occurring spontaneously or following trauma, and to prevent hæmorrhage after tooth extraction or surgical procedures. Arrest of spontaneous hæmorrhage was attempted in Case I (active bleeding into a knee joint) and in Case VII (epistaxis). In both cases the effect of plasma therapy is difficult to evaluate. Hæmarthroses are self-limiting, but the relief of pain during the plasma transfusion was impressive. In Case VII adequate treatment was not given, and it is doubtful if plasma was effective. In Case III, bleeding was occurring from multiple facial lacerations. Plasma therapy was effective in raising the plasma AHF concentration on two occasions, but bleeding continued after the first treatment and ceased during a second treatment three days later.

Plasma was given in four cases for the extraction of teeth. In three (Cases I, VIII and IX), therapy was given before extraction in an effort to prevent bleeding; the patient in Case VI presented with a bleeding tooth socket. Carious teeth are the cause of much morbidity among hæmophiliacs. Extractions are postponed because of the risk of bleeding until pain or infection occurs. A persistent oozing of blood from sockets for weeks after extraction and requiring repeated transfusions is not unusual, and is the cause of lengthy stay in hospital. In Cases VI and IX the patients were mildly hæmophilic. After treatment, the plasma AHF concentrations reached hæmostatic levels, and bleeding was easily controlled. The patient in Case I was moderately affected, and eight extractions were carried out at the one time. Bleeding was never a serious problem; but oozing occurred from three sockets on the third day and required both plasma and blood transfusions. There was further mild oozing on the sixth and tenth days. This patient received optimal plasma therapy, but completely effective hæmostasis was not obtained. In Case VIII inadequate treatment was given. The patient was severely hæmophilic, and one litre of plasma raised the plasma AHF concentration to 7% only. In retrospect, bleeding was to be expected. This patient was probably not suitable for plasma therapy, as we suspect the presence of an AHF inhibitor in his blood.

It is a basic principle to avoid surgery in hæmophilia unless adequate indications are present. One patient (Case II) was mildly hæmophilic, and repeated tonsillar infections were interfering with health and growth. The tonsils were very large and a growth of hæmolytic streptococci was cultured from them. If this patient had been severely affected, we should not have relied on plasma to correct the hæmostatic defect but should have either avoided surgery or attempted to obtain some type of AHF concentrate. Plasma therapy was effective in controlling initial hæmorrhage, but maintenance therapy was not continued for a sufficient time after operation. Plasma was given for 28 hours only. Bleeding commenced 36 hours after operation, but was controlled with further plasma therapy.

The two eye operations in Case IV were uneventful. It is not possible to be certain that bleeding would have been troublesome without plasma therapy. There is little doubt that plasma therapy was life-saving in Case V, that of a severely hæmophilic subject with a ruptured spleen. However, 13 litres of plasma were required over a nine-day period, and we should have used AHF concentrates on this patient if these had been available.

From the foregoing experience, it is our opinion that plasma therapy has a definite place in the treatment of hæmophilia. It is the replacement therapy of choice for patients with mild hæmophilia. Severely affected patients require large volumes of plasma, and even these may not achieve correction of the hæmostatic defect. AHF concentrates of human origin offer more hope for the severely hæmophilic subject, since smaller volumes of fluid need to be administered and higher plasma AHF levels can be maintained (Kekwick and Wolf, 1957).

"Fresh-frozen" plasma has advantages over fresh plasma, particularly when large volumes are required. For elective procedures, plasma of the appropriate blood group can be stock-piled at leisure. However, the AHF concentration of "fresh-frozen" plasma is unpredictable. Despite standard conditions of preparation and storage the preservation of AHF varies greatly, some samples retaining full potency after three months, while others deteriorate in a few weeks. We have not used plasma stored for longer than three months. The variable preservation of AHF in "fresh-frozen" plasma is probably the explanation of the different responses in cases such as Case IV after similar plasma doses on separate occasions. Laboratory control of therapy is essential to check the potency of the plasma administered.

It is important to thaw and agitate "fresh-frozen" plasma thoroughly before administration. Pool and Robinson (1959) showed that AHF could be retained in the bottle along with cold-precipitated fibrinogen. If the plasma is allowed to remain at 37° C. for a short time after complete thawing, the fibrinogen redissolves. Warmed plasma also reduces the incidence of venous spasm. Circulatory overload has not been seen in our cases, even with prolonged therapy. In three cases generalized urticaria occurred, but responded satisfactorily to antihistamine drugs. In two cases (Cases IV and V) serum protein concentrations did not change significantly during therapy.

The simplest method of laboratory control is with the thromboplastin screening test. Crude tests of clotting function, such as the whole-blood coagulation time, are valueless. Thus in Case VIII the whole-blood coagulation time was normal after one litre of plasma when the plasma AHF concentration was only 7%. The thromboplastin screening test is possibly over-sensitive, since

the result remained abnormal in some cases even when bleeding was controlled with plasma therapy. This test may give an abnormal result with a plasma AHF concentration of 40% (Hicks and Pitney, 1957), whereas the results of plasma AHF assay in our cases suggest that bleeding can be controlled often with a plasma AHF concentration between 20% and 30%. However, the screening test is much more rapid than assay techniques and can be carried out by most hospital laboratories.

Summary.

Nine hæmophiliacs were treated during 12 episodes of actual or threatened hæmorrhage with fresh or "fresh-frozen" plasma. Therapy was required for spontaneous or traumatic hæmorrhage, or as a cover for teeth extractions or other surgical procedures. An attempt was made to raise the plasma antihæmophilic-factor concentration to the hæmostatic range during the critical period when the hæmostatic mechanism was under stress. Laboratory control of therapy was found to be essential for intelligent management of the patient.

Acknowledgements.

We are indebted to the Director and staff of the Western Australian branch of the Red Cross Blood Transfusion Service for supplies of fresh and "fresh-frozen" plasma. Mr. M. H. Elliott, A.I.M.L.T., provided valuable technical assistance.

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Reports of Cases.

ABSENCE OF UTERUS WITH POSSIBLE GENETIC DEFECT: REPORT OF TWO CASES.

By ALAN A. JONES, M.B., B.S.,
Saigon, Vietnam.

THE following two cases are thought to be of sufficient interest to report.

Case I.

A Vietnamese woman, aged 25 years, presented herself on December 20, 1959, with the complaint that she had never become pregnant. She had been married for six years. It was also stated that she had never menstruated. There were no other complaints. The interesting family history (in common with that of Case II) is given separately below.

Examination of the patient showed her to be a well-proportioned female with the following proportions: height 59 in., bust 33 in., waist 25·5 in., hips 33·5 in., weight 98 lb. The breasts superficially appeared well developed and normal. No abnormalities were detected on palpation. The external genitalia appeared normal except that there was no pubic hair. The vagina appeared normal. No uterus or cervix could be palpated on manual examination per vaginam; neither could the ovaries be palpated. Speculum examination confirmed the absence of any trace of the cervix. Clinical examination revealed no evidence of endocrine abnormality. There was complete absence of pubic and axillary hair. The cardio-vascular, respiratory, alimentary and nervous systems were normal on clinical examination. There were no apparent abnormalities of the urinary system. Through the cooperation of this patient, opportunity was afforded to examine the second patient.

Case II.

A Vietnamese female, aged 21 years, presented herself and mentioned that she had not yet menstruated. Her family history is given below. Examination showed her to have the following proportions: height 63 in., bust 31·5 in., waist 23 in., hips 32 in., weight 104 lb. Her breasts appeared moderately well developed, and no abnormalities were detected. The external genitalia were of normal appearance, except that the pubic hair was very sparse. On rectal examination, no cervix or corpus uteri and no ovaries could be palpated. The cardio-vascular, respiratory and central nervous systems were all normal on clinical examination. No abnormalities were detected in the renal or alimentary systems.

Family History.

These two patients were members of a family of six sisters. One sister, aged 30 years, is married and has never menstruated or borne children. The patient in Case I said that this sister resembled herself very closely. Another sister, aged 28 years, is married and has three young children. A further sister, aged 23 years, menstruates and has axillary and pubic hair. She recently married, but has not yet become pregnant. The other sister died at the age of three years after a stomach ache.

The mother has five brothers, all of whom are married and have many children each. All the children are normal as far as is known. This mother also has three sisters. One died at the age of 21 years. It is not known whether she ever menstruated. One sister is aged 50 years and is married, but has never menstruated or produced children. The third sister is married and has eight children, six boys and two girls. No further information is available concerning the girls.

The father of the present two patients has six brothers and three sisters. All these have children.

The maternal grandmother had ten brothers and sisters, the sexes being evenly divided. All the sisters had children, but no further information was available concerning these.

This family history can be diagrammatically represented as in Figure I.

Comment.

Total absence of the uterus is in my experience uncommon. I have seen only one other case, also in a Vietnamese woman. The family history is at once striking. The many gaps are to be regretted, but as large families are the rule in Vietnam, this patient did rather well to remember what she could of the family history. It was not practicable to follow up the details of the history with home visits.

The significant fact is that here is a generation containing females incapable of reproduction owing to absence of the uterus, and apparently normal females. In the previous generation, on the maternal side, there are also females incapable of reproduction, presumably owing to absence of uterus, and females capable of reproduction.

This may be explained on a genetic basis. First, these facts may be explained as a somatic defect resulting from a sex-linked gene defect, with varying degrees of penetration. More probably the explanation concerns a mutant

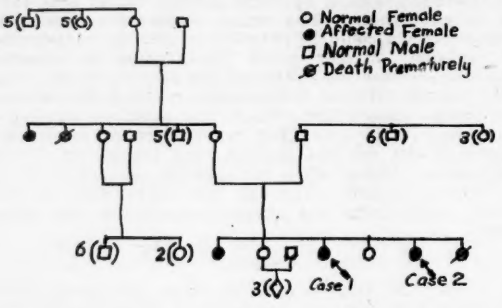


FIGURE I.

gene defect resulting in partial damage to the chromosome influencing uterine development during the meiotic division of the ovum. It is regretted that no medical literature, in English, is available to me here for comparison with similar previous reports.

Reviews.

The Year Book of Medicine (1959-1960 Year Book Series). *Edited by Paul B. Beeson, M.D.; Carl Muschenheim, M.D.; William B. Castle, M.D.; Tinsley R. Harrison, M.D.; Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D.;* 1959. Chicago: The Year Book Publishers, Incorporated. Sydney: W. Ramsay (Surgical) Limited. 7¼" × 4¾", pp. 732, with 110 illustrations. Price: 88s.

THE Year Books of Medicine are like milestones marking the years as medical science progresses, producing a continuing stream of new knowledge, some of it opening up new fields for exploration, some consolidating ground already gained. The current volume, like its predecessors, presents a very informative survey of progress in general medicine during the year under review, in the form of abstracts of most of the important papers which have been published during that period, with occasional editorial comments. The editorial board is unchanged, and the volume is divided into the usual six parts, with Paul Beeson in charge of that on infections, Carl Muschenheim on the chest, W. B. Castle on the blood and blood-forming organs, T. R. Harrison on the heart and blood vessels and the kidney, F. J. Ingelfinger on the digestive system, P. K. Bondy on metabolism. They and the Year Book Publishers are to be congratulated on continuing to provide a valuable service in helping the medical profession to keep itself informed about recent developments.

The Kinetics of Cellular Proliferation. Edited by Frederick Stohlman, Jr., M.D.; 1959. New York and London: Grune & Stratton, Incorporated. 10" × 6¼", pp. 472, with many figures. Price: $5.75.

THIS volume contains the edited proceedings of a conference, sponsored by the Hæmatological Study Section of the National Institutes of Health of the United States, on the fundamental problems and techniques relating to the study of the kinetics of cellular proliferation, which was held at Salt Lake City in January, 1959, under the chairmanship of M. M. Wintrobe. The ground covered by the conference can be briefly indicated by listing the titles of the six sections into which the proceedings are divided. Section I is entitled "The Use of Classic Morphologic Technics", and contains eight papers with the relevant discussions. Section II deals with DNA synthesis, stability and degradation. Section III is on studies with DNA labels, and is divided into two subsections, one dealing with radiophosphorus and radiocarbon labels, and the other with tritium-labelled thymidine. Section IV is about studies on leucocyte and platelet production, and contains one subsection on studies on leucocytes with the use of labels other than DNA and another on the regulation of leucocyte and platelet production. Section V contains eight papers discussing various aspects of the kinetics of the regulation of cell production. Section VI is headed "Mathematical Considerations", and includes 70 pages of severely higher mathematical discussions, heavily laced with pages of complex equations. As may be seen, this volume is strictly for those interested in advanced fields of basic hæmatological study. The standard of production is high, and these papers no doubt include many contributions of fundamental importance.

Stepping Stones to Labour Ward Diagnosis. By R. H. J. Hamlin, 1959. Adelaide: Rigby Limited. 7¼" × 4¾", pp. 163, with 29 illustrations. Price: 10s. 6d.

WITH the current tendency to use the centrally situated obstetric hospitals as "confinement centres" (with various alternative arrangements for the after-care of normal patients at some other location), a very considerable quantity of clinical material passes through the labour-ward unit. Consequently the members of the full-time staff working in such a unit, and especially the medical superintendent, are in a position to acquire a high degree of dexterity, and if the potential is there, to develop first-class obstetrical judgement.

In this booklet Dr. R. H. Hamlin has attempted to pass on to students, nurses and practitioners some of the results of his intensive experience in such a capacity at the Women's Hospital, Crown Street, Sydney. Much of the content of this small volume is devoted to an enthusiastic advocacy of the author's own preferences and techniques, especially in regard to the choice of rectal rather than vaginal examination, and we should have liked to see the book written rather more objectively. Nevertheless, Dr. Hamlin has given us a careful appraisal of the various techniques currently in use for assessing, both before and during labour, the likely or actual progress of the birth. Famous names are brought together, and Smellie, Munro Kerr, De Lee, Chassar Moir and Windeyer are freely quoted in an attempt to incorporate all that is best in the teaching of these exponents with current thought and experience. The illustrations take the form of bold line drawings and are particularly effective. Altogether this very moderately priced book achieves its objective and is a worthwhile contribution to the important subject of intrapartum diagnosis, especially in those instances in which there is some departure from the normal state of affairs.

Tools of Biological Research. Edited by Hedley J. B. Atkins; 1959. Oxford: Blackwell Scientific Publications. 9" × 6", pp. 200 with 113 illustrations. Price: 37s. 6d. (English).

THIS book is a collection of papers presented in 1958 at a symposium of the Surgical Research Society, London. The purpose of the papers is to familiarize the medical graduate with modern research instruments and techniques. The twelve subjects presented are discussed by persons distinguished for their research work in these fields.

Only two contributions deal with truly biological techniques—tissue culture (H. B. Fell) and tissue transplantation (L. Brent). Both contributions are simple but comprehensive accounts of these topical subjects. However, the quality of the illustrations in those sections is poor, the plates being too small and poorly reproduced. P. Armitage makes a short but sound summary of the problem of the design of adequately controlled experiments.

The remaining contributions cover a wide assortment of technical procedures, ranging from electron microscopy to flame photometry and electromanometry. In each, attention is concentrated on the physical principles underlying the technique, and little space is devoted to its potential applications. Some of the chapters make difficult reading, for the electrical, mechanical and mathematical principles underlying each technique are discussed at length. These details are probably inadequate as a complete course of instruction for the person about to use the technique for the first time, and are disturbingly irrelevant for the general reader.

For those who are gadgeteers, this book will make fascinating reading, but it fails in its second purpose, that of indicating the scope and limitations of such instruments in an integrated biological investigation.

The Medical Journal of Australia

SATURDAY, OCTOBER 22, 1960.

MEDICAL UNDERGRADUATE EDUCATION IN VICTORIA.

For some years concern has been expressed about the shortage of doctors in Victoria, a shortage that has been regarded as not only current but also to be anticipated in the immediate future, and indeed in the remote future if something drastic is not done about it. In 1955 a subcommittee of the Victorian Branch of the British Medical Association reported that there appeared to be a deficiency of approximately 200 medical practitioners in the State, that an additional 179 new graduates were required each year to maintain the (then) present position and that the supply of graduates from the university during the next five years would not meet that requirement. In a further report, dated February 9, 1960, an ad-hoc committee of the Branch concluded that there was still a shortage of doctors in Victoria, that existing and planned facilities would not overcome that shortage and that it was urgently necessary that further facilities for the training of medical students be established. Between the publication of these two reports, in 1958, the *Monash University Act* was passed, and in June of that year the Interim Council of Monash University held its first meeting.

The Council of the new university was charged with the development of a balanced university, but at the same time was required to give priority to those faculties which were most severely overtaxed at the University of Melbourne and to have regard to the urgent needs of the community for scientists and engineers. At that time a quota operated in the Faculty of Medicine at the University of Melbourne, and shortly afterwards quotas were established in many subjects of the science and engineering courses. The priority determined therefore was as follows: (*a*) Science, Engineering and Medicine (concurrently), (*b*) Arts, (*c*) Commerce, (*d*) Applied Science, (*e*) Education, (*f*) Law; and on this the Interim Council based its planning for the development of the university. Early consideration was given to the ultimate size of the proposed medical school, and the Council determined that the annual intake into the first (pre-medical) year should be 120, with the following anticipated numbers in the five subsequent academic years: 100, 75, 65, 60, 60. These facts were published in a report from the Interim Council dated February 23, 1960. Discussing the type of medical school, the report emphasized the necessity for a medical school to be incorporated as an integral part of the university and at the same time for the clinical school to be an integral part of the medical school. Therefore it was accepted that in ultimate development the teaching hospital and the medical school must be established in close proximity to the university campus. Interim proposals provided for facilities for the first (pre-medical) year to be available at Monash University from 1961 onwards. It was planned to erect buildings for pre-clinical instruction during 1961, 1962 and 1963. Clinical instruction would commence in 1964. No plans had been developed as yet for erection of the teaching hospital since, at the time of the writing of the report, the necessary finance was not in sight. An arrangement had therefore been made with the committee of management of the Alfred Hospital for the carrying out of clinical instruction with certain provisos. Finance was assured for the building of the first section of the science block, which was expected to be completed by October, 1960, and would be ready for the commencement of first year classes, including first year medicine, in 1961. The pre-clinical schools of anatomy, physiology and biochemistry with provision for microbiology had been developed in outline and were planned for construction through the 1961-1963 triennium in such a way as to provide progressively for the needs of the medical school. The cost of those buildings and facilities would be £1,577,000. The proposal was already before the Australian Universities Commission, and it was anticipated that their support would be forthcoming in a recommendation to the Commonwealth Government for financial aid.

Yet another committee which has been active in this field is the Medical Education Committee appointed by the Victorian Government on February 5, 1960. This committee, consisting of Dr. J. H. Lindell (Chairman), Mr. R. R. Blackwood, Sir Albert Coates, Professor S. Sunderland and Sir William Upjohn, has acted with commendable expedition. Its terms of reference were broad:

> To inquire into, report upon, and make recommendations, including comments upon the magnitude and urgency of any proposals concerning the following matters:
>
> (1) Medical undergraduate education in Victoria, particularly as it concerns metropolitan teaching hospitals.
>
> (2) How the existing hospitals, and those at present proposed, may best be utilized for clinical and/or other teaching in association with the two universities —Melbourne and Monash.
>
> (3) How may the existing hospitals, and those at present proposed, be brought into teaching association with the University of Melbourne, and/or Monash University, in the most expeditious and efficient manner, having due regard to economy.
>
> (4) What will be the effect of the establishment of the proposed Monash University Medical School upon the State hospital building programme; whether the programme will need to be materially altered, and if so, to what extent and at what stage.
>
> (5) Any other matters which appear to be relevant to the inquiry.

Seized with the urgency of the situation, the Medical Education Committee made an interim report to the Premier of Victoria on May 24, 1960. The principal recommendation of that report was that Monash University

be asked to provide for the maximum possible intake into the pre-medical year in 1961—up to 120 students—and that to permit Monash University to take that number of students (approximately 60 students more than the number originally proposed) the necessary financial provision be made by the State Government and the Australian Universities Commission to allow appropriate extensions to be made to the science block at Monash University during 1960. The main report of the Committee, dated August 3, 1960, has now been made available, and elsewhere in this issue (see page 670) we publish in full the recommendations which it contains. These recommendations speak for themselves. They are comprehensive and practical and provide a coordinated plan covering the whole field of the medical schools and hospitals involved.

We are not very clear just how far the recommendations of the Interim Committee of the Monash University have been accepted in detail by the Victorian State Government or to what extent the funds necessary to put them into operation have been or are likely to be made available from the Commonwealth Government through the Australian Universities Commission. However, it looks as if something will be done, so far as the Victorian Government is concerned, if we may judge by the published comments of the State Premier[1] on the report of the Medical Education Committee. He was reported as having stated that the report would be implemented and that financial requirements could be met fully. A standing committee was to be appointed as recommended. Action had already been taken to enable Monash University to double the intake of medical students for 1960 up to 120 students and to proceed with the science block during 1960. This is encouraging, offering a major promise of advance in the provision of facilities for training those who desire to enter a medical course in Victoria and ultimately supplementing the supply of doctors for that State. Whether it will be soon enough and sufficient in scope to provide adequately for the medical needs of the people of Victoria is still an open question, but it is unlikely that it will be. Since all planning for medical undergraduate education in Victoria seems to be based firmly on the principle that the numbers in any one medical school should be kept rigidly within a conservative maximum figure, serious thought needs to be given without delay to the question of a third medical school in Victoria.

[1] *The Age*, August 19, 1960.

Current Comment.

SMOKING AND THE CARDIO-VASCULAR SYSTEM.

SMOKING was introduced into our Western world by the sailors of Christopher Columbus in 1492 when they found the Indians of San Salvadore smoking tobacco rolled in maize husk. During the subsequent 300 years, tobacco was chewed, snuffed and smoked in pipes until the first cigar factory was erected in Hamburg in 1788. Cigarettes were introduced in France and from there spread to most parts of the world by about 1850.

The effects of tobacco and its main alkaloid nicotine on the heart and peripheral circulation have been studied for over a century. In 1848 R. J. Graves published his findings of disturbed heart action resulting from heavy smoking. During the following decades many writers described chest pain resulting from use of tobacco, which led to the introduction in 1899 by H. Huchard of the term "tobacco angina". The knowledge available a few years ago was summarized in a report by the Committee on Smoking and Cardio-Vascular Disease set up by the American Heart Association published in 1956. This discussed certain effects such as acceleration of heart rate, rise in blood pressure, reduction in peripheral blood flow and electrocardiographic changes, but concluded that the evidence available at that time did not justify acceptance of a cause and effect relationship between smoking and ischæmic heart disease. A great deal of work since then, pharmacological, epidemiological and clinical, has revealed new evidence which has now been reviewed by this Committee.[1]

L. M. Bargeron *et alii*[2] studied the effect of cigarette smoking on coronary blood flow and myocardial metabolism in human volunteers. They were successful in catheterizing the coronary sinus in 14 instances and were thus able to measure coronary blood flow by the nitrous oxide desaturation method as well as myocardial usage of oxygen, glucose, pyruvates, lactates and ketones. Cigarette smoking in these normal subjects caused a significant rise in coronary blood flow and decline in coronary vascular resistance with diminished myocardial consumption of oxygen and glucose. The evidence that cigarette smoking does not reduce coronary blood flow in normal individuals is in agreement with observations that electrocardiographic and ballistocardiographic changes are absent in normal subjects, but are present in patients with coronary heart disease, suggesting that such individuals respond to smoking by decrease in coronary blood flow. This hypothesis receives support from animal studies by S. H. Rinzler *et alii*[3], who found that nicotine increased the coronary flow in a normal rabbit heart, but when such an animal had been made atherosclerotic, nicotine resulted in decline in coronary blood flow.

Important pharmacological work has been done by J. H. Burn and his group in Oxford.[4,5] They confirm the findings that the direct effect of nicotine is to dilate coronary blood vessels, but at the same time nicotine powerfully stimulates the supraoptic nucleus in the hypothalamus leading to discharge of vasopressin from the posterior lobe of the pituitary gland and hence coronary vasoconstriction. The direct effect of nicotine on the isolated atrium of the heart of rabbits was transient inhibition, abolished by atropine, followed by excitation due to the release of noradrenaline and adrenaline from stores within the heart. They furthermore demonstrated that stores of these amines could be depleted by treatment with reserpine thereby preventing the stimulating action of nicotine.

Epidemiological studies surveying mortality data from large populations published during the last few years demonstrate, with few exceptions, an increased mortality in smokers due to coronary artery disease. J. F. Dorn[6] followed carefully 198,926 Veterans Administration policyholders for whom smoking data and cause of death information could be obtained. According to Dorn the death rate from coronary artery disease was 63% higher in cigarette smokers than in non-smokers; no such increase was found in cigar and pipe smokers. Similar results were obtained by E. C. Hammond and D. Horn[7] who studied total death rates and causes of death in relation to 187,783 men who were traced for an average of 44 months. The general mortality rate was 70% higher in cigarette smokers than in a comparable group of non-smokers, and death rates from coronary heart disease were also far higher in regular smokers. Buechley *et alii*[8]

[1] *Circulation*, 1960, 22:160 (July).
[2] *Circulation*, 1957, 15:251 (February).
[3] *Amer. J. Physiol.*, 1956, 184:605 (March).
[4] *Proc. roy. Soc. Med.*, 1957, 50:500 (July).
[5] *Brit. med. J.*, 1958, 1:137 (January 18).
[6] *Publ. Hlth Rep. (Wash.)*, 1959, 74:581 (July).
[7] *J. Amer. med. Ass.*, 1954, 155:1316 (August 7); 1958, 166:1159 (March 8).
[8] *Circulation*, 1958, 18:1085 (December).

studied 3994 longshoremen in California and concluded that the difference in death rates between non-smokers and smokers showed a strong and constant relationship between cigarette smoking and coronary heart disease mortality, at least in men 40 to 70 years of age.

Clinical studies by C. B. Thomas and E. A. Murphy[9] concentrated mainly on the ballistocardiographic smoking test, which demonstrated marked changes in blood pressure, heart rate, stroke volume and cardiac output after the smoking of one cigarette. The results were sufficiently reproducible for use as a screening test to classify young adults according to their patterns of circulatory reactivity. Young subjects with a family history of hypertension showed a significantly greater rise in cardiac output than was expected. In the offspring of parents with coronary disease, however, a reduction in stroke volume and cardiac output was demonstrated.

Having reviewed the above information, the Committee on Smoking and Cardio-Vascular Disease of the American Heart Association states that the evidence "strongly suggests that heavy cigarette smoking may contribute to or accelerate the development of coronary heart disease or its complications". No attempt is made, however, to answer the important question so frequently asked by our patients as to whether abstinence from smoking after the occurrence of a heart attack is likely materially to improve prognosis. One cannot help feeling that the report, whilst focusing attention once again on the problem of smoking and the cardio-vascular system and neatly summarizing recent work, has gone only a little way towards answering many practical problems.

EFFECTS OF CANCER CHEMOTHERAPEUTIC AGENTS ON THE HUMAN FŒTUS.

ONE result of the growing importance of cytotoxic agents in the treatment of various forms of malignant disease is that cases are now occasionally seen in which their use may be indicated when malignant disease is complicated by pregnancy. Though fortunately uncommon, this is a particularly tragic situation when it occurs, and in such cases the probable effect of the cytotoxic agent on the fœtus becomes of the greatest importance. This problem is discussed in a recent paper by J. E. Sokal and E. M. Lessmann.[1] They point out that chemotherapeutic agents used in cancer fall into several categories—alkylating agents such as nitrogen mustard, antimetabolites such as 6-mercaptopurine, specific mitosis-blocking agents such as desacetylmethylcolchicine and various tissue poisons. All exert their greatest damaging effect on tissues with a rapid rate of cell division, and it might therefore be expected that the fœtus would be especially vulnerable to them. The effect of various chemotherapeutic agents on the course of pregnancy and on the fœtus has, in fact, been extensively studied in various animals, and it has been shown: (i) that most cancer chemotherapeutic agents can cause fœtal death and many can cause congenital malformations in fœtuses not killed; (ii) that the effect on the fœtus often depends on the exact time in pregnancy when the drug is administered; and (iii) that though doses employed were in most cases much above those employed clinically, in some cases death or malformation has been caused by doses within the clinical range. There is also a certain amount of clinical evidence on the subject, and Sokal and Lessmann have been able to collect 50 cases in which cancer chemotherapeutic agents were administered to women during pregnancy, and the effect on the fœtus was recorded.

Among the antimetabolites, the drug most fully documented in this regard is aminopterin, because J. B. Thiersch used it in 24 published cases to induce therapeutic abortion. In a first series of 12 patients spontaneous abortion occurred in 10 cases, but in 2 pregnancy had to be terminated surgically; a second series was less fortunate in that while in 6 cases abortion occurred spontaneously, in 5 pregnancy was terminated surgically, and in one the pregnancy was allowed to go to term, resulting in an anencephalic fœtus. Some of the fœtuses recovered in the first series also had severe malformations. Two other cases have been reported in which aminopterin was self-administered during pregnancy; in each case the pregnancy went to full term, with the birth of a seriously deformed infant. On the other hand two cases are known in which the closely allied drug, amethopterin ("Methotrexate") was administered in the second and third trimesters without apparent harm to the infant. Aminopterin and amethopterin are folic-acid antagonists, and it is not surprising that they should have an adverse effect on the fœtus; they were introduced for cancer chemotherapy because folic acid is known to be necessary for normal embryonic development in the rat. (These two drugs have been used with striking success in the treatment of chorionepithelioma, and are also used in the treatment of some types of leukæmia.)

There was surprisingly little evidence that any of the other cytotoxic drugs about which clinical data are available had any adverse effects on the fœtus. One case is recorded in which a woman was treated for chronic myelocytic leukæmia with alternating courses of busulphan and 6-mercaptopurine throughout pregnancy; an undersized (3 lb.) infant was born, with multiple congenital abnormalities, which survived for two and a half months; at the autopsy, the most striking histological findings were widespread changes in cell nuclei, with frequent bizarre nuclei observed in many tissues. In a somewhat similar case, in which busulphan was administered throughout pregnancy, the infant born at full term was undersized (4 lb. 6 oz.) but otherwise normal, and was developing normally three years later. In two other cases in which treatment was with 6-mercaptopurine throughout pregnancy, in one case in combination with other cytotoxic drugs, apparently normal premature infants were born; however, both failed to survive. Two cases are recorded in which desacetylmethylcolchicine was administered throughout pregnancy; in each a normal infant was born, though one died at the age of two years of cirrhosis of the liver; however, this was thought to be accounted for by post-natal circumstances.

On the other hand quite a number of cases have been recorded in which nitrogen mustard or other alkylating agents were administered, in some cases early in pregnancy, without any apparent ill-effect on the infant subsequently delivered, and in several other instances other cytotoxic drugs given during the second and third trimesters had no apparent ill-effect on the fœtus. The eldest of the children delivered after such a pregnancy was nearly ten years old when the last report was made, but most of them are much younger, and the possibility of late ill effects cannot be excluded. It is clear that the data so far collected are inadequate for any firm conclusions to be drawn, apart from the undoubted toxicity of the folic-acid antagonists. It also seems evident that the stage of pregnancy at which treatment is initiated has an important bearing on the outcome. In animal experiments cancer chemotherapeutic agents were found to be most damaging to the fœtus during the middle third of pregnancy, but this result is obviously not applicable to the human case, in which damage to the fœtus is in nearly every case associated with the administration of drugs during the first trimester. In surveying their data, Sokal and Lessmann express surprise that the human fœtus should be so resistant to potent cytotoxic agents, and they comment that the use of some cancer chemotherapeutic agents during pregnancy may not be as hazardous as has generally been assumed, especially if treatment is deferred until after the first trimester. However, sufficient has been said to show that, in cases in which the exhibition of cytotoxic drugs during pregnancy may appear to be indicated for the mother's sake, the decision in the present state of knowledge is a difficult one. It seems likely that many would take the view that, if pregnancy is to be allowed to continue, the use of cytotoxic drugs is contraindicated, at least during the first half of pregnancy.

[9] *J. chron. Dis.*, 1958, 8:202 (August).
[1] *J. Amer. med. Ass.*, 1960, 172:1765 (April 16).

Abstracts from Medical Literature.

OPHTHALMOLOGY.

Transient Myopia after Acetazolamide.

J. F. Muirhead and H. G. Scheie (*A.M.A. Arch. Ophthal.*, February, 1960) report a case of severe and transient myopia as a result of oral administration of acetazolamide to reduce fluid retention in pregnancy. The increase in myopia was approximately 7·5 dioptres. The patient had a total of 500 mg., two tablets one week apart, and increased myopia appeared within 24 hours of the second dose. The authors point out that only one case of myopia due to acetazolamide has occurred in a patient with glaucoma. The authors are unable to be sure of the mechanism which produces the myopia. Possible mechanisms which have to be considered are accommodative spasm, changes in the refractive power of the lens, aqueous and vitreous, and stretching of the sclera.

Subconjunctival Administration of "Soframycin".

D. Ainslie and J. E. Cairns (*Brit. J. Ophthal.*, January, 1960) describe the subconjunctival use of "Soframycin" in 30 cases of corneal infection. The "Soframycin" was dissolved in distilled water, or 1/5000 adrenaline (400 mg. per ml.) A single dose contained 100 to 500 mg., and in some cases this was repeated daily for three days. In 19 cases there was no bacteriological confirmation of the type of infection, due to previous use of topical antibiotics. In 16 cases infection followed injury to the cornea by a foreign body. The results of treatment were mostly satisfactory. In 21 cases improvement was rapid, in seven it took place more slowly, and in two not at all. In no case did the injection cause any untoward reaction, and there was little pain associated with the injection.

Peripheral Iridectomy in Closed-Angle Glaucoma.

P. L. Blaxter and S. Chatterjee (*Brit. J. Ophthal.*, January, 1960) discuss their experiences with peripheral iridectomy in closed-angle glaucoma. Certain criteria are necessary to determine cases suitable for this procedure. Gonioscopy must show the angle to be open; the longer and more frequent the attacks, the more likely the angle is to be closed; the presence of field and disc changes would indicate permanent damage to the angle; and if ocular tension is raised between attacks there must be permanent damage to the angle. The authors believe that cases of chronic closed-angle glaucoma should be treated medically if there are no disc or field changes, but should surgery become necessary, then peripheral iridectomy will remove the danger of an acute attack and may even cure the condition. The operation is difficult to perform if the tension is high and it is suitable only for cases in which the tension has been controlled medically. The operation may be successful in advanced chronic closed-angle glaucoma if the raised tension is due to iris contact alone; however, in these cases one must be prepared to perform a filtering operation at a later stage. In early closed-angle glaucoma, with congestive attacks with normal tension between attacks, there is usually an excellent chance of complete cure. In the glaucomatous eyes, especially those whose fellow eye has had an acute attack, a cure is certain with peripheral iridectomy. Finally, the operation is indicated and successful in eyes which show no evidence of glaucoma, provided the angle is narrow, but whose fellow eye has had an acute attack. The authors have performed peripheral iridectomy in over 70 eyes. In this series peripheral iridectomy has controlled the disease in all but three cases.

Œstrogens in the Prevention of Secondary Hyphæma.

J. L. Goldberg (*A.M.A. Arch. Ophthal.*, June, 1960) presents evidence to show that conjugated œstrogens prevent secondary hæmorrhage in traumatic hyphæma. Sixty-three patients with traumatic hyphæma were studied. The treatment was the same in all except that 22 patients received in addition conjugated œstrogenic substances administered intravenously on admission to hospital and œstrogenic tablets for several days thereafter. In children the dose was 10 mg. intravenously on admission to hospital and then 1·25 mg. orally four times daily for five to seven days. Older patients had double this dose. The dosage was the same for both sexes. In the control group, 12 of the 41 patients had secondary hæmorrhage, with loss of vision in eight. In the group treated with conjugated œstrogens there was no secondary bleeding or need for surgical intervention in any of the 22 cases. There were neither ocular or systemic side effects. It would appear that the therapy was of value in preventing secondary hæmorrhage.

Pierre Robin Syndrome.

J. L. Smith *et alii* (*A.M.A. Arch. Ophthal.*, June, 1960) report on seven cases of the Pierre Robin syndrome, in four of which there was bilateral ocular disease. The Pierre Robin syndrome is characterized by micrognathia, cleft palate and glossoptosis. There is difficulty in breathing and nursing. The ocular defects were congenital glaucoma in two cases, bilateral retinal disinsertions with retinal detachment in a third case, and severe congenital myopia in another case. It is suggested that in all cases of Pierre Robin syndrome an ophthalmological examination should be made under general anæsthesia.

Alpha-Chymotrypsin in Cataract Surgery.

R. G. Murray and S. M. Dravce (*A.M.A. Arch. Ophthal.*, June, 1960) compare cataract surgery as done with and without using alpha-chymotrypsin. When using the enzyme, the authors found that as the zonular fibres weakened the lens assumed a more spherical shape and it was impossible to grasp the capsule with forceps. In the latter part of the series the lens was fixed immediately after the injection of the enzyme. It was found that the easiest way of fixing the lens over a period of time was by using an erysiphake. It was also noticed that after injecting the enzyme there was loss of vitreous even before the eye was touched in some cases. There was marked corneal reaction in nearly all cases in which the enzyme was used, but this usually cleared considerably by the tenth post-operative day. As the series progressed, it was found that complications were more prevalent in the enzyme series, and so the use of the enzyme was restricted to selected cases. The authors are of the opinion that the enzyme should be reserved for the younger age group (30 to 60 years), the extraction should be with an erysiphake, and suture should be chromicized gut or silk.

Tubular Fields due to Glaucoma: Results of Operation.

J. Laval (*A.M.A. Arch. Ophthal.*, May, 1960) produces evidence to refute the belief that glaucoma patients with tubular fields deteriorate after operation to reduce tension. The author discusses 15 patients with fields no greater than 10° at the greatest meridian. The ages of the patients varied from 38 to 70 years. Trephine was performed on two eyes, iridectomy on one, iridencleisis on nine, and cyclodiathermy on one. In not one patient was there deterioration of vision or of visual field after operation. Some of the patients did lose field by delaying operation and were saved from blindness only by operation.

Corneal Lenses in Ophthalmic Practice.

H. Agatston *et alii* (*Amer. J. Ophthal.*, February, 1960) review the question of contact lenses and state that their widespread use is creating a major problem in eye care. The authors list the advantages of contact lenses as follows: cosmetic and psychological advantages, increased field of vision, better visual acuity, less aniseikonia in monocular aphakia, magnification in myopia, no fogging of lens in mist and rain, and greater safety as compared with spectacles. The indications for their use are aphakia, keratoconus, irregular astigmatism, therapeutic, vocational and psychological. The contraindications are absence of a clear indication, unsuitable personality of the patient, cases with marked epiphora or excessive dryness, ocular infection, ocular allergies, local neoplasm, degenerations of the cornea, corneal œdema, lenticular astigmatism, corneal anæsthesia and presbyopia. Difficulties in their use may be due to the lens being too loose, too tight, too flat or too steep, or to the wrong refraction. The authors consider that contact lens fitting should be an integral part of ophthalmic practice.

Long-Term Results in Glaucoma Therapy.

P. A. Chandler (*Amer. J. Ophthal.*, February, 1960) reviews 20 patients with glaucoma who had been followed for many years. These patients include some cured with surgery alone, some controlled by medical means only, some in whom surgery was unsuccessful and medical therapy had to be continued, and some with low-tension glaucoma successfully treated by opera-

tion. The author concludes that eyes with advanced glaucoma with marked cupping of the disc and gross field loss withstand increased tension poorly and require a low tension to prevent further loss of function. Eyes with limited cupping withstand increased tension better than eyes with total cupping of the disc, while eyes with normal disc withstand increased pressure well. The appearance of the disc therefore may give an indication as to treatment; the eyes with a normal disc may withstand a tension of 30 mm. of mercury or more for many years. Whatever the stage of the disease, an operation which reduces tension to a low enough level will probably prevent further loss. In pseudoglaucoma with considerable field loss, if tension is lowered by operation then the disease may be arrested.

The Radioactive Phosphorus Test in Ophthalmology.

P. L. CARMICHAEL AND I. H. LEOPOLD (*Amer. J. Ophthal.*, March, 1960) report further observations on the use of radioactive phosphorus for the detection of malignant intraocular disease. The patient is given 500 μc. of radiophosphorus. After one hour counts are made at the 3, 6, 9 and 12 o'clock positions. The readings in each quadrant are of one minute's duration and an average of these counts is then obtained. The counter is placed over the area of the suspected lesion and the region of highest uptake determined. Counts are again repeated after 24 and 48 hours. Of 134 cases, 17 incorrect results were obtained, an accuracy of 86%. However, eight lesions were not accessible to the anterior probe, and if these are omitted, the accuracy is 90%. Results with the posterior probe for detecting posterior pole lesions have not been encouraging. The test should not be performed on pregnant women or children. The test has its limitations, and is to be regarded as an adjunct to clinical examination.

Effects of Phospholine Iodide on Intraocular Pressure in Man.

S. M. DRANCE AND F. CARR (*Amer. J. Ophthal.*, March, 1960) have tested the effect of phospholine iodide (217M1) on normal human eyes and its hypotensive effect on glaucomatous eyes. In normal eyes a drop of 0·25% phospholine iodide produced a pronounced fall in intraocular pressure. The average fall in pressure was 55%. There was also an increase in facility of outflow. Miosis commenced in one hour, there were conjunctival vasodilatation, blurring of vision and browache. Fifty-nine glaucomatous eyes were treated with phospholine iodide with a satisfactory drop in intraocular pressure in 57. The average fall of intraocular pressure in 59 eyes was 48%. Side effects were identical with those described in normal eyes. In two patients severe epigastric cramps, nausea and vomiting, cold sweats and a general feeling of prostration occurred. These were relieved with an injection of atropine sulphate.

Demecarium Bromide in the Treatment of Glaucoma.

N. KRISHNA AND I. H. LEOPOLD (*Amer. J. Ophthal.*, March, 1960) report on the use of demecarium bromide (BC-48) in various types of glaucoma. BC-48 is a powerful synthetic cholinesterase inhibitor It p sesses certain muscarinic properties, is soluble in water, and stable for indefinite periods. It produces rapid and prolonged miosis, accompanied by congestion of the eye, spasm of accommodation, and ciliary pain. The miosis of BC-48 is abolished by atropine and homatropine, and BC-48 induces miosis in atropenized and homatropinized eyes. The authors record their experiences in treating 106 glaucomatous eyes of 59 patients with BC48 over a period of six months. Control was considered to have been achieved when for a period of four months tension never exceeded 25 mm. of mercury and there was no loss of visual acuity, no further loss of visual field, no new peripheral anterior synechiæ, increase in coefficient of facility of outflow above 0·16 c.mm./min./mm. of mercury, no increase in cupping, and no complications due to the therapy.

Acrylic Anterior Chamber Implants for Uniocular Aphakia.

D. P. CHOYCE (*Amer. J. Ophthal.*, March, 1960) gives a detailed account of the correction of uniocular aphakia by means of an all-acrylic anterior chamber implant. The subject is discussed under the following headings: why an implant should be used; what sort of implant should be used; how an implant should be used; what complications may be encountered; what percentage of success can be expected; and finally the impact which this work has on more general problems encountered in ophthalmology. The author discusses in detail the preoperative management of these cases, contraindications to the use of the anterior chamber implant, the details of the operation, and the post-operative care and possible complications.

OTO-RHINO-LARYNGOLOGY.

Chemoreceptor Tumours in the Neck.

R. DALLACHY AND I. C. SIMPSON (*J. Laryng.*, April, 1960) state that the collections of chemoreceptor cells which form the carotid, aortic and pulmonary bodies have proved physiological functions. Other aggregations occur in the glomus jugulare and in the superior and inferior ganglia of the vagus. Many small glomera are found close to the walls of arteries in the muscles throughout the body. Neoplastic change is more frequent in the larger collections. Tumours of chemoreceptor tissue in the neck arise most frequently from the carotid body (361 recorded cases). In recent years a few have been found which originated in the ganglion nodosum of the vagus nerve (13 recorded cases). Four cases have also been reported in which the site of origin was outside these organized collections of glomus cells; one of these is described in the present paper. These neoplasms are encapsulated. Microscopically they consist of "epithelioid" tumour cells in small solid masses with variable amounts of collagenous stroma which surrounds groups of cells, but not individual cells; blood vessels are numerous. Multiple tumours are fairly common, but only one malignant tumour with blood-borne metastases has been described. The commonest clinical feature of a growth arising in the ganglion nodosum is a mass presenting in the lateral aspect of the neck behind the angle of the mandible; it is usually continuous with a swelling in the lateral wall of the pharynx which displaces the tonsil medially. A carotid body tumour gives rise to an external cervical mass which is situated at a lower level and is rarely associated with an internal swelling. Neoplasms originating outside the carotid body and the ganglion nodosum may give rise to either external or internal swellings. The treatment of tumours arising outside the carotid bodies should be excision, although this will be followed by recurrent laryngeal nerve paralysis when the tumour originates in the ganglion nodosum or in the trunk of the vagus. Intracranial extension does not occur, and provided that the whole tumour can be removed without damage to vital structures, recurrence does not take place.

Infant Tracheostomy.

L. P. GRAY (*J. Laryng.*, March, 1960) presents some interesting facts regarding the size of the tracheostomy tubes. He points out, for example, that the metal cannula size French 18 has an external diameter of 6 mm. but an internal airway diameter of the inner tube of only 3·5 mm. This is important, because he quotes Gabriel Tucker as saying that, in infants, the subglottic diameter was between 6 and 8 mm., and 5 mm. was too small and 4 mm. actually a stenosis. Therefore, the number 18 French is actually equivalent only to a stenosed trachea. The author also lists several other disadvantages of metal tracheostomy tubes. He also presents a method of using a harness to hold a new type of plastic "Polythene" infant tracheostomy tube which he has developed. He states that the external diameter is 6 mm. and the internal diameter 5 mm. Also, it is non-irritating. There is an appendix giving some details of the method of making this type of tracheostomy tube.

Vasodilators for Labyrinthine Vascular Insufficiency.

J. C. SEYMOUR (*J. Laryng.*, March, 1960) has treated cases of vascular insufficiency of the laybrinth with the newer vasodilators. He reports that the results are most encouraging, especially in cases where, hitherto, little was contemplated or expected. This is especially so, for example, in cases of sudden perceptive deafness, notably in young people, and good restoration of part of their hearing loss has obtained serviceable hearing for them. In Ménière's disease, the author suggests that, as these patients are often of an anxious, tense make-up, judicious use of tranquillizers coupled with vasodilators may prove to be the more efficient treatment. There is also a large group in which the labyrinthine insufficiency forms part of a more general vascular insufficiency, or may be heralding such. These need full and careful investigations as indicated. Treatment of the general condition will often help the labyrinthine disability, sometimes to a marked extent.

Medical Education.

MEDICAL UNDERGRADUATE EDUCATION IN VICTORIA.

THE following are the recommendations of the Committee on Medical Undergraduate Education in Victoria appointed by the Government of Victoria on February 5, 1960. The recommendations are contained in a report of the Committee to the Premier and Treasurer of Victoria dated August 3, 1960.

RECOMMENDATIONS.

(The matriculated students proceed to the university to undertake the medical course. In the first year, known as the premedical year, they study subjects such as physics, chemistry and biology, etc. Those students who pass proceed to the preclinical year, where they commence study of anatomy, physiology and biochemistry. Normally of 200 students who enter the premedical year, 160 will proceed to the preclinical years. After two years' study in preclinical subjects, students pass to the clinical years, which are undertaken, in the main, in teaching hospitals; pathology and microbiology are studied at this stage.)

(1) That the provision for training medical students in Victoria be substantially increased:

(a) to meet the established need for additional doctors in Victoria now and in the future;

(b) to permit suitable and appropriately qualified students, who might otherwise be excluded, to take the medical course in Victoria.

(2) That in order to give effect to this programme, a second medical school be established.

(3) That the second medical school be established in association with Monash University.

(4) That Monash University be asked to provide for the maximum possible intake into the premedical year in 1961. (this is expected to be up to 120 students—approximately 60 more than the number originally proposed); and that to permit Monash University to take this number of students, the necessary financial provision be made to allow appropriate extension to the science block at Monash University during 1960.

(5) That Melbourne University maintain its premedical year admission rate at 200 students per annum. Recent experience indicates that this rate will give an intake into the preclinical year of approximately 160 students per annum, which should be maintained until Monash University has established its preclinical intake at 120 students per annum. Ultimately the combined preclinical intake to both Universities should reach a figure of 280 students per annum.

(6) That ultimately a complete medical school and teaching hospital be established on Monash University site.

(7) That with this end in view (see recommendation 6) the preclinical departments be established on Monash University site forthwith, being so placed as to adjoin the teaching hospital when that is built. These departments must be completed in time to receive students in 1962.

(8) That in the meantime, University departments of pathology and microbiology be established at the Alfred Hospital so as to be ready to receive students in 1964.

(9) That a teaching hospital be built on Monash University site when the community service need for such a hospital is established. The Committee estimates the need as such that the building will not be commenced prior to 1970.

(10) That for general clinical teaching purposes, Monash University be associated primarily with the Alfred and Prince Henry's Hospitals and if the need arises (for general clinical teaching purposes) with the Queen Victoria Memorial Hospital; and that the University of Melbourne be associated with The Royal Melbourne and St. Vincent's Hospitals.

(11) That the association of Hospitals mentioned in recommendation 10 with Monash University, be a permanent and continuing one, by agreement between the University and the Hospitals, to be dissolved, if the need arises, only by agreement between those bodies.

(12) That subject to agreement between Monash University and The Queen Victoria Memorial Hospital on the future constitution and organization of the Hospital, that Hospital be associated with Monash University for obstetrical and, to some extent, gynæcological teaching—the remainder of the gynæcological training to be provided (if necessary) by the Alfred and Prince Henry's Hospitals. Further, that The Queen Victoria Memorial Hospital be associated with Monash University for general and pædiatric clinical teaching by agreement, and according to the needs of Monash University.

(13) That The Royal Women's Hospital be associated with the University of Melbourne and The Royal Melbourne and St. Vincent's Hospitals for obstetrical and, to some extent, gynæcological training. At such time as the Mercy Hospital obstetrical unit is established, this will provide obstetrical and some gynæcological training for St. Vincent's Hospital students; thereafter, The Royal Women's Hospital will be associated with The Royal Melbourne Hospital for obstetrical and gynæcological teaching purposes.

(14) That when additional obstetrical hospital beds are required for community service needs, i.e., beds additional to those mentioned in recommendation 13, these beds be provided at the Alfred Hospital, Monash University Hospital (when that hospital is ready) and at Prince Henry's Hospital as land becomes available.

(15) That in the meantime, the Hospitals and Charities Commission be asked to review the hospital building programme in the light of these recommendations and in the present context, particularly as they affect The Royal Women's Hospital rebuilding programme.

(16) That for pædiatric training the Royal Children's Hospital be associated with the University of Melbourne, The Royal Melbourne and St. Vincent's Hospitals; and Monash University with the Alfred, Prince Henry's and The Queen Victoria Memorial Hospitals. If Monash University needs cannot be met from these three hospitals, Monash University should negotiate an interim agreement with the Royal Children's Hospital, which Hospital has indicated its willingness to provide clinical pædiatric training.

(17) That the Alfred Hospital rebuilding programme proceed as planned, provided:—

(a) that provision be made for early establishment of University departments of pathology and microbiology; and

(b) that the plan be such as to permit provision, in the future, of preclinical and clinical departments adjoining the Hospital buildings, if the need for these departments is manifested.

(18) That the question of departments to be provided at Prince Henry's Hospital be pursued by Monash University and the Hospital, but:

that Crown land in the immediate vicinity of Prince Henry's Hospital, currently leased to industrial firms, be taken up by the Government as leases expire and made over to Prince Henry's Hospital for additional teaching and service facilities.

(19) That additional service and teaching facilities required at The Queen Victoria Memorial Hospital by 1964 be investigated at once with the Hospital by Monash University and the Hospitals and Charities Commission, and put in hand as soon as possible.

(20) *That a Standing Committee be appointed by the Government to make recommendations upon medical education generally and particularly as it affects the teaching hospitals.* Without being representative in character, this Committee must include those persons best qualified by training and experience to advise the Government on this important subject.

(21) That the Standing Committee should, at the outset of its deliberations, consult the Government Statist and thereafter work in close liaison with his office for the purpose of establishing reliable statistical information for the future guidance of the Committee. The Committee considers that this action is not only desirable but very necessary if the medical educational needs of the State are to be met.

(22) That the Standing Committee referred to in recommendation 20 be requested to investigate the quality and quantity of clinical teaching material available in hospitals, and to make recomendations thereon.

In particular it should examine the suggestions raised in the body of this report (paragraph 89) for improving the quality of clinical material, and recommend thereon. It should too, be invited to investigate and make recommendations upon other matters suggested in the body of this report.

(23) That although the Universities, and the teaching hospitals associated with them, are aligned with medical schools north and south of the city, there should not be any direction or zoning of students from any localities to one University Medical School or the other. Admissions to either school should be unrestricted by geographical considerations.

(24) That there should be complete reciprocity between the two Universities as far as this concerns the transfer of students from one University to the other, subject to agreement between the two Universities upon standards. It is most desirable that there should be reciprocity between the Universities at every level of medical education, and that equal status and standing should be accorded to graduates of both Universities.

(25) *That the State Government request the Commonwealth Government to provide additional scholarships for tertiary education* to permit more students, who might otherwise be precluded for financial or social reasons, to undertake the medical course.

(26) That the Universities be asked to discuss with the appropriate education authorities the possibility of having the premedical year taken by students as part of secondary school education. In particular, the Committee recommends that the trial or pilot scheme mentioned in the body of this report (paragraph 32) be investigated by these authorities and if it is possible, put into operation.

(27) *That in view of the re-alignment of teaching hospitals with the Universities, a University Department of Surgery be established at The Royal Melbourne Hospital in time to take students by 1964.*

(28) That the Governing Board of Monash University Campus hospital (when that hospital is established) be comprised of 12 members appointed by the Governor-in-Council, as follows:—

6 persons selected from a joint panel of names submitted by Monash University and the clinical schools associated with it;

3 persons qualified as "contributors" to the hospital within the meaning of the Hospitals and Charities Act elected by persons so qualified;

3 other persons.

The hospital should be registered as a "separate institution" under the provisions of the Hospitals and Charities Act and, as such, should be subsidised by the Hospitals and Charities Commission for hospital purposes, and financed by the Univerity for teaching purposes.

(29) That Monash University campus hospital be a "closed" hospital, that is, a hospital wherein only those doctors may practise who are duly appointed to the hospital staff upon the recommendation of an advisory board generally constituted in keeping with existing advisory boards at other teaching hospitals; further that other teaching hospitals should be "closed" hospitals in the same sense. The Committee recommends that the existing Regulations under the *Hospitals and Charities Act* 1958 should be appropriately amended to permit this course.

(30) That the Standing Committee referred to in recommendation 20 be requested to investigate the present arrangements under which patients are admitted to the Cancer Institute, and to investigate with the Board of the Institute, and the boards of the teaching hospitals, means by which medical education concerning cancer could be improved.

Hospital Building Programme.

(31) That—

(a) no small hospitals should be built which would interfere with the ultimate determination to build Monash University Hospital. The Committee is informed that prior to the decision to build Monash University, a hospital was envisaged in the Moorabbin area; the hospital at Monash University will provide for this area and Monash University should endeavour to enlist the support and aid of local people to assist in the University hospital project;

(b) in general, because of the steady drain upon clinical teaching material from the teaching hospitals, the Committee considers that small hospitals, that is, of fewer than 200 to 300 beds, should not be built in the metropolitan area;

(c) the Southern Memorial Hospital and Sandringham Memorial Hospital, for which plans are already in hand, should be proceeded with, but that their size should be kept to the smallest consistent with Governmental obligations to the local communities;

(d) the Alfred Hospital rebuilding programme be proceeded with as expeditiously as possible and incorporate departments of pathology and microbiology as parts of Monash University Medical School;

(e) the size and scope of activities of The Royal Women's Hospital be reconsidered by the Hospitals and Charities Commission and the Committee of Management of the Hospital in the light of the recommendations of this Committee;

(f) the necessary service and teaching additions to The Queen Victoria Memorial Hospital be put in hand so that they will be completed prior to 1964, when this Hospital will be required for clinical teaching by Monash University.

(32) That the Government make a public announcement as soon as that is possible, to inform students and others interested, of the Government's policy towards medical education and particularly the effect that this will have upon student intake to the medical course in 1961. This will permit students to make their plans in time to make application for either University should they so desire. The Government should too, ask the Universities to formulate their own policies and to make these public as soon as possible for the same reason.

The Committee, in framing its recommendations, and suggesting a timetable for various stages in the Monash University programme, has been necessarily guided and influenced by the information before it. If the recommendations are accepted, they must be financed, and the ability of Monash University to adhere to its programme depends upon the amount of money available to the University and the associated hospitals for capital and maintenance requirements. Another factor could affect the recommended programme; this is the ability of Monash University to obtain the staff necessary for its needs.

These are evidently matters for the University to determine as soon as possible; they are mentioned in the present context to emphasise their importance and to stress the need for early action if the University is to have a reasonable prospect of adhering to its schedule.

British Medical Association.

VICTORIAN BRANCH: SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on July 20, 1960, at the Alfred Hospital, Melbourne. The meeting took the form of a series of clinical demonstrations by members of the medical staff of the hospital.

Pitfalls in Electrocardiography.

DR. H. B. KAY and DR. JAMES M. GARDINER demonstrated examples of pitfalls in electrocardiography due to faulty technique, to defects in the recording apparatus and to misinterpretation of *T*-wave changes due to causes other than coronary disease. With regard to technique, they emphasized correct lead connexions, switching and labelling, elimination of alternating current interference by correct earthing, and abolition of tremor and movement. A wandering baseline could be due to an unstable recording machine, loose connexions and poor lead application and sweating.

Adequate lead application was particularly important in the chest Leads V2 and V3, faulty application of which

could lead to simulation of bundle branch block and of a pattern of acute myocardial damage.

Machine defects could produce a variety of misleading tracings, which included general slurring, slurring of the *QRS* complexes, slurred *S-T* depression with low *T* waves, *S-T* elevation simulating acute pericarditis, and terminal dipping of the *T* waves simulating early changes of myocardial ischæmia or infarction. Illustrations were given of all these faults, and examples were shown of underdamping, of electrical overdamping and of overdamping due to excessive stylus pressure in direct writing machines.

Finally, examples were shown of *T*-wave flattening or inversion not due to coronary disease, but commonly confused with it. It was emphasized that those changes could occur in leads 2, 3 and aVF in normal people, and they could occur in the left-sided chest leads in some thin-chested individuals. Changes might be due to fear, fever, nervous tachycardia, ice-cold water or sweating.

Electrolyte disturbance such as hypokalæmia could cause important changes, as could anæmia, myxœdema, Addison's disease, beriberi, alcohol and drugs such as "Chloroquine", emetine, digitalis and quinidine. In addition, changes simulating those of coronary disease could occur with right-heart strain or with left-heart strain due to hypertension or to aortic or mitral-valve disease.

The Treatment of Severe Hypertension.

DR. A. J. BARNETT outlined the principles governing the treatment of hypertension, with respect to the criteria for diagnosis of the condition, indications for treatment, preliminary assessment of patients, and the most useful drugs in the management of hypertension and the method of using them. He showed charts on the results over the past nine years of treatment of patients with severe hypertension with ganglion-blocking drugs and other hypotensive drugs. The charts showed the survival rates in patients with papilloedema ("malignant phase") and without papilloedema ("benign phase"), and the progress of the hypertensive disease in the brain, eyes and heart. The benefit from treatment was shown by the increased survival rate among patients with papilloedema in comparison with the expected rate without treatment, and by improvement in ocular and cardiac status. Pictures of ocular fundi, radiographs of the chest and electrocardiographic tracings from individual patients showed the improvement with treatment.

Films of Operative Procedures.

Herniorraphy.

DR. ROBERT S. LAWSON showed three cinematographic films in colour with sound-track commentary illustrating operative procedures.

The first operation was a herniorrhaphy for a direct inguinal hernia with a tubular sac. The sac was excised and closed at the neck. Then the gap in the fascia transversalis of the posterior wall of the inguinal canal was repaired with interrupted sutures of thread. The aponeurosis was then plicated behind the cord according to the method of Wyllys Andrews, the cord being left external to it.

The second operation was a herniorrhaphy for a very large oblique inguinal hernia. After ligation of the sac at the neck, the cremaster muscle, stripped off the cord, was approximated over the posterior wall of the inguinal canal. Then the strips of fascia lata were darned between the conjoined tendon and the ligament of Poupart, passing up to encircle the emerging cord at the internal ring. The aponeurosis was again plicated behind the spermatic cord.

Sphincterotomy.

The third operation was a sphincterotomy for fissure-in-ano of long standing, the consequence of hæmorrhoidectomy performed many years before, apparently with inadequate after-treatment. Spasm and stricture had caused a narrow, painful anal orifice, not even admitting the little finger-tip. The fissure was excised, and the subcutaneous external sphincter in its base was isolated, lifted up and divided. The mucosal gap was then repaired with catgut. About a month later it was possible to pass a full-sized proctoscope without pain or difficulty. The patient was passing normal stools for the first time in years.

Mammary Duct Ectasia.

PROFESSOR MAURICE EWING said that mammary duct ectasia was an uncommon condition which usually affected the aging breast. To begin with there was no more than symptomless dilatation of the terminal ducts. That might infrequently be felt as a vague tumour under the areola; in a minority of cases there would be a brownish discharge from the nipple. As the condition progressed, the nipple tended to become retracted. At that stage the ducts might rupture, and the fatty débris which escaped incited an inflammatory reaction. If that was acute, an abscess developed close to the areola; more often the cellular response was a chronic one, and the periductal tissues became packed with plasma cells (plasma-cell mastitis). At that stage there was an obvious firm lump deep in the areola with fixation to the skin, and often, too, there were enlarged nodes in the axilla. The condition mimicked cancer very closely, even in sections, when the divided ducts often exuded thick toothpaste-like material and the diagnosis of comedo-mastitis first suggested itself. The ætiology of the condition was not fully understood, but it seemed likely that it was no more than a variant of chronic mastitis.

Plummer-Vinson Syndrome.

DR. J. WATTS said that in Plummer-Vinson syndrome (or more correctly, Paterson Brown-Kelly syndrome), characteristic epithelial changes were observed in association with low serum iron values, and often with hypochromic anæmia. Those changes were manifest as koilonychia, cheilosis, atrophic glossitis and œsophageal web formation with associated dysphagia. That the epithelial lesions in the upper part of the gastro-intestinal tract could be superseded by malignant change had been commonly recognized. Four cases of the syndrome with associated carcinomas of the cheek, tongue, hypopharynx and œsophagus had been observed. Therapy with iron had been demonstrated to produce a regression of the epithelial lesions; prevention of the later malignant changes would therefore seem to depend on the adequate and prolonged administration of iron to the patients.

Photographs Taken at Endoscopy.

DR. GEORGE BERCI gave a demonstration of colour photographs taken through a variety of endoscopic equipment. He said that such records were of considerable help in documentation and also in teaching. The same equipment could be used for a moving photographic record.

Ophthalmological Conditions.

DR. PERCY H. COWEN showed several patients to illustrate ophthalmological disorders.

The first was a patient with vertical incomitant or paretic squint due to trauma. Dr. Cowen said that the patient had right inferior oblique muscle paresis, with increase in the angle of squint on looking up to the left.

The second patient was a child with left concomitant convergent squint. Dr. Cowen said that, in contrast to the previous case, the angle of squint was unchanged in all directions of gaze. The patient also demonstrated the accommodative factor in a convergent squint, as the eyes became parallel when she put on her glasses, which corrected a hypermetropic refractive error.

Dr. Cowen's third patient had had a detachment of the retina of the left eye cured by diathermy operation four years previously. The scar of the diathermy barrage could be seen as a large white patch in the upper nasal part of the retina.

The fourth patient had asteroid bodies in the vitreous; they could be seen floating about as the eye moved. They did not interfere with visual acuity. The patient had also had a Kirby's operation for senile entropion.

Other conditions discussed by Dr. Cowen were senile macular degeneration and circinate retinopathy associated with senile macular degeneration.

DR. JAMES FOSTER showed a series of patients illustrating the ocular effects of diabetes, hypertension and glaucoma. He also showed patients with corneal grafts and ocular injuries.

The Management of Deafness.

A demonstration was arranged to illustrate the measures that could be undertaken to overcome the particular defects in hearing found in the various forms of deafness.

DR. J. G. H. REFSHAUGE illustrated the patterns of hearing loss associated with the different types of deafness, and indicated the appropriate means of treatment.

MR. L. C. WOOLLEY, the hospital's Honorary Audiometrician, demonstrated the different types of hearing aids available at present, and indicated the principles governing

the selection of the most suitable appliance for any particular individual.

MR. PETER FREEMAN dealt with the surgical treatment of conductive deafness. Specimens to illustrate the normal anatomy of the middle ear and the techniques involved were shown with the aid of the operating microscope. Two cases of chronic suppurative otitis media and mastoiditis were discussed. The first case shown illustrated the preservation of good hearing with the eradication of the disease. The second case illustrated the eradication of the disease, and the restoration in hearing that could be effected by a tympanoplasty.

Three cases of successful mobilization of the stapes for otosclerosis were presented, and the indications and results of that procedure were discussed.

The Surgery of Atrial Septal Defect.

MR. G. R. STIRLING presented a demonstration based on 47 cases of atrial septal defect in which operation had been performed by the Thoracic Surgery Unit at the Alfred Hospital in the last two years. The anatomical types were illustrated by drawings and specimens. The commonest lesion was a defect in the position of the fossa ovalis (septum secundem defect), less commonly the defect lay high in the septum adjacent to the superior vena cava, and rarely it lay low in the septum near the tricuspid valve. Any of those defects might be associated with anomalous connexion of the right pulmonary veins to the right atrium or superior vena cava. Nine cases of "sinus venosus" defect were encountered, in which a high defect was associated with anomalous pulmonary venous drainage into the superior vena cava.

Mr. Stirling said that the symptoms were rarely dramatic; they consisted of effort dyspnœa, palpitations and fatigue. The clinical signs were characteristic — a hyperdynamic right ventricle, a pulmonary systolic murmur, wide and often fixed splitting of the second heart sound and occasionally a tricuspid mid-diastolic murmur at the left sternal edge. The electrocardiogram showed right axis deviation and right bundle branch block. The chest radiographs revealed cardiac enlargement, prominence of the pulmonary artery and pulmonary plethora. The diagnosis had been proved by cardiac catheterization in most cases.

After experience with several methods, the present policy was to use the atrial well technique for repair in most cases, whilst if there was any doubt about the precise nature of the lesion the pump oxygenator would be preferred. The advantages of the atrial well technique were that it was simple and safe and did not require large quantities of blood. It had proved to be particularly useful in the repair of sinus venosus defect in nine cases. Since 1958, 44 patients had been operated on by that technique; there had been one death in the series. During the same period, in a further three cases successful repair had been achieved by the use of the pump oxygenator.

Mr. Stirling said that in view of the proven safety of the method, it was probable that operation is indicated in most cases of atrial septal defect in which the left-to-right shunt constituted 50% or more of the pulmonary blood flow. When atrial fibrillation, moderate pulmonary hypertension or congestive heart failure was present, operation should be strongly advised. Operation was contraindicated for patients with a small shunt with little hæmodynamic upset, because the prognosis without treatment was excellent. Patients with clinical cyanosis and those with severe pulmonary hypertension who were still acyanotic had nothing to gain from surgery, and the operative risk was prohibitive.

Urinary Infections in Children.

MR. E. DURHAM SMITH discussed, with charts, photographs and X-ray films, an approach to the investigation and management of the commoner causes of urinary tract infection in children. He said that as urinary tract infections were frequently seen in practice, it was impracticable to investigate each patient fully. Some indications had been found helpful in deciding which children required further urological study. He suggested that reasonable indications for detailed investigation were: (i) the occurrence of one attack of infection in a male child; in a male it was rare not to find some demonstrable cause for the infection; (ii) a third attack in a female child; the first two attacks could be treated symptomatically, but a third would indicate the need to look for a cause; (iii) relapse after adequate therapy with the correct antibiotic; (iv) a more severe attack associated with hæmaturia or albuminuria; (v) pyuria in association with central nervous system signs.

Mr. Durham Smith then said that the diagnosis of urinary tract infection must be definitely proved by cultures of urine taken under sterile conditions—catheter specimens from females and mid-stream specimens from males. It was a frequent practice to label as "urinary tract infection" a child with malaise, fever, frequency and scalding and urgency of micturition and cloudy urine, the latter being an ordinary specimen collected under non-sterile conditions into a bottle or pot. Such symptoms were frequently encountered in emotional children or might occur in vulvitis, etc., and did not necessarily incriminate the urinary tract.

Mr. Durham Smith then said that when the diagnosis had been established by culture, and the indications for investigation were present, some guiding principles could be laid down as to the order of investigations. For instance, in a female, especially if the result of the double micturition test was positive, a micturating cysto-urethrogram rather than an intravenous pyelogram should be taken first. That was because the commonest cause of urinary tract infection in a female was vesico-ureteric reflux, a phenomenon not revealed by an intravenous pyelogram. On the other hand, in a boy intravenous pyelography was the first diagnostic test, as the commonest causes of infection in that sex were to be found in problems of hydronephrosis. The indications for panendoscopy and retrograde pyelography with estimation of emptying times would depend on the results of those tests. Mr. Durham Smith stressed that in childhood no patient could be said to have been fully investigated without a micturating cysto-urethrogram. A whole range of diagnostic possibilities were unravelled by that test, which were not revealed by an intravenous pyelogram.

Mr. Durham Smith then discussed the causes of urinary tract infection. He said that stasis of urine was the basis of most infections. Stasis could be (a) mechanical or obstructive, or (b) functional, in which case no organic obstruction could be demonstrated. Examples of the mechanical group were well known — posterior urethral valves, urethral polyps, foreign bodies in the bladder (mainly in young girls), bladder diverticula, intrinsic or extrinsic strictures of the ureter, especially at the pelvi-ureteric junction, stenotic or sphincteric ureteroceles and calculi. X-ray films and operative specimens of those conditions were shown and methods of management were discussed. Mr. Durham Smith said that in children as compared with adults, relatively much greater emphasis was placed on functional stasis, the causes of which were less well known. He showed examples of several types. In urethral diverticula, there was no obstruction to the passing of urine but residual urine in the diverticulum resulted in pyuria. The neurogenic bladder was a relatively common cause of infection, especially from the various forms of spina bifida. The commonest cause of functional stasis in females was vesico-ureteric reflux. That might occur both in normal-calibre ureters and in megaureters. Its great importance lay not only in its frequency, but also in the relative ease of its management by non-operative means—namely, multiple micturition. Stephens had studied the problems of double ureters in his authoritative papers. Double ureters which opened independently into the bladder and did not allow reflux did not cause urinary infection, but double ureters with reflux did. Similarly, double ureters which conjoined above the bladder might produce reflux from one ureter to the other, and did not adequately empty down the common stem. Mr. Durham Smith demonstrated that phenomenon by means of a cineradiograph from a girl, aged seven years, subsequently treated by partial nephrectomy. Finally, examples of functional hydronephrosis and hydroureter were shown.

The Seldinger Technique of Angiography.

DR. H. A. LUKE discussed 225 studies of the aorta and of its branches carried out in the hospital by the Seldinger technique of angiography, and showed a number of radiographs. He said that in that technique a "Polythene" catheter was inserted into an artery, without exposing it, by the use of a needle in the artery to insert the special guide wire; the needle was then removed and replaced with the catheter. Owing to the fact that the tip of the catheter was of the same diameter as the guide wire, it could be inserted without difficulty; the remainder of the catheter could be considerably larger than the original needle. The femoral, carotid or brachial arteries could be employed, and the catheter could then be inserted in either a proximal or a distal direction. Dr. Luke showed examples of all the possible combinations. He said that in the 225 cases there had been no deaths and no serious complications. The precautions to be observed mainly concerned the necessity for gentle handling of the guide wire and catheter.

Out of the Past.

THE MELBOURNE HOSPITAL, 1854.

[From the Seventh Annual Report of the Committee of Management of the Melbourne Hospital, 1854.]

BEFORE concluding their Report, the Committee feel compelled to bring prominently under notice the expenditure of the past year, and the financial position of the Institution for the present.

That the outlay has been large they candidly admit; but they are prepared to show that not a single shilling has been expended needlessly or without sufficient cause. With regard to the principal items of increase, viz.—wages, meat, bread, groceries, vegetables, the Committee remark that the enormous increase in the number of patients will, to a great extent, account for these. Formerly the services of a Resident Surgeon were found sufficient for the wants of the patients, but in the month of September last the Physicians and Surgeons unanimously recommended the appointment of an Assistant House Surgeon. With this recommendation your Committee at once complied, and Mr. James who had for some time acted as Apothecary, being upon examination found competent, was promoted to the office; Mr. Curtis being appointed Apothecary in his stead. Again the filthy state in which the Hospital was at the time the present House Steward took office, the little attention paid to patients, especially during the night, compelled your Committee to authorise the employment of additional Nurses, Wardsmen, and Servants, thereby incurring further expence [*sic*], not only in the matter of wages, but also increasing the consumption of the necessaries of life. But independent of these circumstances, the Governors will recollect the great rise in the price of meat which took place in May last. At that period this article suddenly rose to 8d. per lb., and although now reduced to 4½d., it continued for a length of time to cost 6d. per lb. In addition, it may be mentioned that the consumption of bread by the patients is much greater than it formerly was: the Medical Officers now generally direct the supply of a good generous diet for the sick, and it has been the anxious desire of the Committee to have the instructions of the faculty strictly complied with. Thus, at considerable expense, eggs have been provided for those whose state of health prevented them from taking other food; while milk and vegetables, instead of being articles rarely tasted by the patients, have been regularly supplied. In thus administering to the wants of the patients, your Committee feel that they have but barely discharged their duty; sick persons, more than others, require constant attention and liberal treatment, and they refused to allow mere motives of economy to interfere with the procurement of such articles of diet as were considered by the Medical Officers essential to the recovery of the diseased.

Obituary.

CEDRIC WATSON GRAY ROCHE.

WE are indebted to DR. H. BOYD PENFOLD for the following account of the career of the late Dr. C. W. G. Roche.

Cedric Roche, well known for his surgical work for forty years, died suddenly from a coronary occlusion on May 5, 1960, at the age of 70 years, while holidaying at Magnetic Island with his wife.

Cedric Roche was born at East Melbourne on April 26, 1890. His mother, still vigorous at the age of 95, survives him. His father, a bachelor of arts of the University of Melbourne, was a Government inspector of officers in charge of stores. Through his foresight his three children had university educations, two medical and one dental.

Cedric was educated at Scotch College, from where he gained a non-residential scholarship to Ormond College. He entered the University of Melbourne in 1907. He graduated at the age of 21 in 1911, and was placed fourth in his final year. While a resident at the Melbourne Hospital he became severely ill with septicæmia from an infected hand. Forty-five incisions were made in his hand and arm before he finally recovered after six weeks in hospital. He was forever grateful to his honorary, the late Mr. Fred Bird, for the successful result. He went to his parents' home to convalesce and exercise his fingers, and there resumed his violin playing that he loved so much for many years. He, his wife and children for years frequently enjoyed Sundays with their own music. After leaving the Melbourne Hospital he was resident at the Children's Hospital, the Women's Hospital and the Eye and Ear Hospital.

In 1914 he volunteered for active service, and for a year frequently tried to get into the Australian Army Medical Corps, but he was refused, as there was a great over-supply of medical officers for the few posts available.

He married Mabel Smith, a sister at the Melbourne Hospital, in 1917, and took up duties for a short time at the Beechworth Mental Hospital. He acted as *locum tenens* for the late Mr. Garnet Leary, and then bought a practice at Ivanhoe, where he stayed three years. It was here that his only son, Austin, was born. Austin became a navigator, and was shot down and killed in a bombing raid over Germany in 1944. Both he and his wife never quite recovered from this loss. Cedric's desire to go fishing and shooting with his many friends lessened, and his pleasures were never quite as enjoyable as previously. His daughter, Betty, became a physiotherapist, and married Hugh Morrow of Ballarat. They have two lovely vigorous boys, of whom Cedric was very fond and proud.

While at Ivanhoe, Cedric obtained his M.S. (Melbourne), his M.D. having been obtained earlier. In addition to his general practice, he was on the acting surgical staff of the Melbourne Hospital and a lecturer at the University of Melbourne. All this work was too much for him, and in 1919 he broke down with laryngeal and pulmonary tuberculosis. He hurriedly sold his practice and went into a sanatorium at Mont Albert, where he did not speak for three months. While convalescing in the country at Box Hill, he developed double pneumonia, but recovered and built his home at Balwyn, where he lived for the rest of his life.

His home was on three acres of land, and when he built it, it was surrounded by dairy farms. He kept a cow to help restore his health, and later horses for himself, his wife and his two children. His first year at Balwyn was spent largely in bed on account of his tuberculosis.

He commenced practice in Collins Street in 1920. His medical friends, knowing his great surgical ability, would appeal to him to get out of bed and do an operation for them, and they would do the after-care. This was the way his private surgical practice started. When he finally recovered, he continued the sharing of duties consistently till the end of his days. He would argue that if he could pass over the surgical after-care of a patient to his own doctor to suit his own health, and if he would go to the country as he did and do operations of election and then leave the patient in the hands of his own general practitioner, he would certainly be consistent and do the same thing in the city. In fact, if patients came direct to him, their own doctor was called in for the after-care. He almost always refused to do it if things went straight ahead, but if there were any complications, I know of no one who visited more frequently and acted more decisively to speed the patient's recovery. I chose him myself when I had my gall-bladder removed, and my confidence was so great and his skill so good that I went home on the fourth day and convalesced, fully clothed, shopping, driving the car and walking in the garden. I asked him if I could do my own after-care, to which he heartily agreed, although he felt I was a bit hasty.

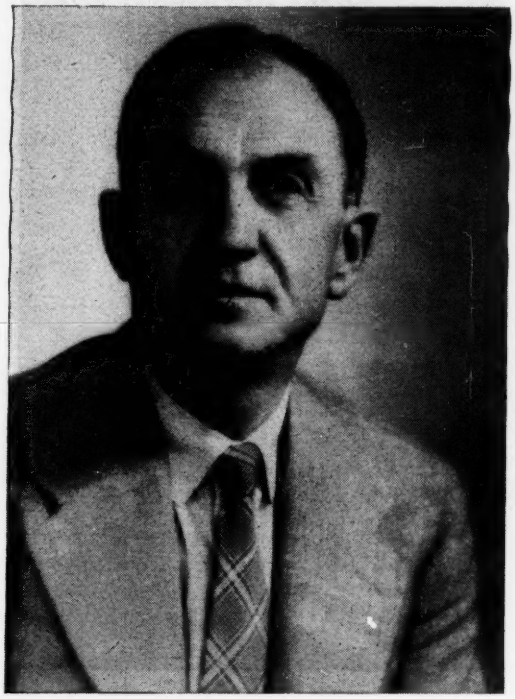
This division of surgical work and therefore division of fees, but never secret division, brought him to blows with the majority of other surgeons, but his integrity was unimpeachable.

I first met him 24 years ago over a toxic goitre. The patient and her husband demanded Mr. Roche and no other. When he asked me if I would do the after-care, I said I knew only a few points in the after-care and therefore was not competent to do it. He replied that he knew no more, and would be readily available if I was worried. I then pointed out that the patient demanded him, and that I had tried to influence the patient to accept a surgeon I knew; he thought that was a natural and right thing for me to do. Here our friendship started, and it increased steadily until the end. He was the nicest man I ever knew or ever hope to know.

At the outbreak of the last war he offered for service but was refused. However, in his private practice he and his anæsthetist did not charge any man who needed an operation to get into the armed forces, or any dependant of

anyone serving his country. Whether they could afford to pay or not, he refused to accept payment. He even went so far as to pay the patient's chemist bill if it was substantial.

For many years he did three to five operations per day all over Melbourne. Technically one could find no better. Temperamentally he was superb. He was extremely kind, and a gracious gentleman to all. He did a wide variety of general surgery, but as the specialists in the different fields developed, he passed his bone and chest work to them and confined himself to abdominal and genito-urinary surgery. He was very quick, but extremely careful, so that apart from prostates he had very few complications; but when they arose he was magnificent, thoughtful and decisive. Although he always safeguarded another doctor's prestige, his own prestige was entirely disregarded. The risk to the patient's life was the only thing that mattered. A stronger yet more



humble colleague in difficult situations one could not imagine. He put years into writing a surgical textbook that was never finished, but now is in the library of the Victorian Branch of the B.M.A. in Melbourne.

He lost heart over the jealousies displayed by many of his fellow surgeons. Although aggressive in his surgery, he was extremely humble, and any moves against him hurt him severely.

In 1937 he went to the Mayo Clinic and the Lahey Clinic, and was greatly impressed by and appreciative of the way in which he was received, their methods of work, their teaching and their selection of surgeons. His only slight disappointment was that he did not think the Thompson resectoscope used at the Mayo Clinic was up to the standard claimed. However, he closely read their writings for the rest of his life. He often said that their short articles on the salient features and without padding should be the standard of medical writings, and pointed out that often the important points of a subject could be "written on a visiting card".

After his sister, Dr. Thalia Roche, died in childbirth in 1927 at the age of 29, he made a grant to the University of Melbourne for a lectureship in obstetrics.

Surgery was his life, but engineering was his main hobby. He was equipped with tremendous quantities of metal and wood working machinery. He got great joy cutting gears or doing other difficult engineering. His equipment was crammed into the space normally occupied by four motor cars. His own personal library was full of books on a wide variety of subjects—politics, philosophy, art, gardening. He loved his garden. He lost his first wife in 1958 from a coronary occlusion, after a long trying period of invalidity from Parkinson's disease. He remarried in 1959, his second wife being Doris Reid, who had been his secretary for 28 years.

Cedric Roche was clear-thinking in all matters, and was fully prepared and equipped for any emergency. The confidence he gave patients and his calm approach to problems was an example to all of us. He often said that old age was humiliating and that he would hate to be bed-ridden or have a slow death, so his final ending was the way he would have chosen if he had had the choice.

DR. DAVID ROSEBY writes: Death has removed from our midst one of the gentlest men of our city. As a surgeon and gentleman, Cedric Roche possessed the attributes of a great man. Graduating from our medical school with the degrees of M.D. and M.S., he achieved success when illness had almost ruined him.

Quite imperturbable, he mastered the difficulties of surgery with a skill that was, at times, breath-taking. When the specialist surgeon started to come into his own, Cedric welcomed the innovation with enthusiasm. Prior to that time he would remove a pituitary tumour with the sang-froid as he would do a resection of a stomach on the same morning.

We general practitioners found in him a friend who would operate on a less privileged member of the community for no fee at all, with the same spirit of cooperation as on one who could afford his moderate fee. No one was less equipped than he to withstand the controversy that was engendered by those who "misunderstood" him. Although he was accused by others of unethical conduct, and always behind his back, never once was his name before the ethics committee. If it had been, I should have known. He invited his detractors to debate his procedures at a big meeting in our hall, and none of them, although present in force, were courageous enough to come forward to speak their piece, and there were great names in his field of practice in those days.

In his non-surgical life he was a lover of the arts and a great reader. When misfortune came to his wife and son, he bore his trials with a fortitude and equanimity that made us admire him the more. Those of us who knew him are all the poorer for his passing.

DR. BRUCE CLAREY writes: I had the privilege of being associated with the late Mr. Cedric Roche over the last nineteen years. Although I was only a fifth-year medical student at the time when I met him, he permitted me to assist him whenever the opportunity arose. Over the next few years I had ample time to appreciate his greatness as a surgeon, teacher and man.

As a surgeon he had a flawless technique which was a pleasure to watch, and in his gentle handling of living tissues he had no equal. He had the ideal temperament for surgery, and no matter how tough the going I have never known him to become ruffled or in any ways lose his natural equanimity.

As a teacher he had considerable ability, and to those who wished to learn he was only too glad to give the benefit of his knowledge and experience. Some years ago he gave me a typewritten draft of a book on which he was working, and which was unfortunately never published. His style, like that of A. K. Henry, makes the reading a pleasure, and at the same time one gets a clear, practical and commonsense exposition on surgery. The teaching of surgery in Melbourne would have been the richer had he been attached to our public hospitals.

As a man, his kindliness and courtesy were well known throughout every private hospital in Melbourne, and it is no exaggeration to say that no other surgeon was so well liked and respected by the nursing staffs as he. In his passing we have lost a great surgeon and one of nature's gentlemen.

DAVID BRAHAM ROSENTHAL.

WE are indebted to DR. H. MAXWELL JAMES for the following account of the career of the late Dr. D. B. Rosenthal.

The tragic and untimely death of Dr. Rosenthal in a motor accident on July 25, 1960, was a shock to all members of the staff of the Tuberculosis Branch of the Health Department in Victoria, and in fact to all members of the

medical profession in Australia interested in diseases of the chest. He was a recognized authority in this specialty.

He was born in Ballarat in 1902, and after a medical course full of honours graduated from The University of Melbourne in 1925. He then served as a resident medical officer at the Royal Melbourne Hospital, where his reputation was high. After this he held various appointments in Melbourne teaching hospitals, and also a residency at the Austin Hospital. He took his M.D. degree in 1927, and later did post-graduate work in London, where he qualified as M.R.C.P. in 1932. Later, in 1958, he was admitted as a Fellow of the College of Chest Physicians of the U.S.A.

On the recommendation of Dr. J. Bell Ferguson, the then Director of Tuberculosis, he returned to Australia to take up the position of Medical Superintendent of Gresswell Sanatorium in 1933. He remained there unti 1950. From 1950 to 1957 he was Deputy Director of Tuberculosis in Victoria, whilst still retaining supervision over Gresswell Sanatorium. In August, 1957, he was appointed Director of Tuberculosis for Victoria, which position he retained until his death. He lost his life in a motor-car accident, while returning from a visit to the Sale Tuberculosis Chalet.

In 1933 Gresswell was a bare shell awaiting the admission of patients. From that time on it was not possible to think of Gresswell without thinking of Dr. Rosenthal and vice versa. From bare boards, this sanatorium developed through many stages until it became without question the best-known sanatorium in Australia, an institution most difficult to fault, and bearing comparison with any in the world. For 24 years, the guiding hand behind this development was that of David Rosenthal. It might be said that he put everything he had into making Gresswell as near to a perfect sanatorium as possible. He maintained this interest even after his appointment as State Director of Tuberculosis in August, 1957. For the last three years he devoted the same intense interest to the tuberculosis scheme of Victoria as a whole, and it might be said that he died in harness.

David Rosenthal was a man of high ideals, and he brought the same steadfastness of purpose into everything he did. There was nothing he detested more than dishonesty, especially of thinking, and many a decision of policy hinged on whether an argument would stand up to what he considered was the essential question: "Is this for the benefit of the patients?"

It has been said that Rosenthal ran Gresswell with a rod of iron. Undoubtedly he was a strict disciplinarian, but it was admitted by the most recalcitrant of his patients that he was always fair. On looking back over the years, it can now be seen that every step he took, every change he made, was always for the ultimate good of the patient. The patients themselves regarded him with deep affection coupled with respect.

Perhaps the outstanding feature of Gresswell is its occupational therapy and vocational training. Rosenthal considered that the day of a patient's rehabilitation began on the day when he entered the sanatorium, and that every patient should be usefully employed. Twice-yearly displays were held of articles made by the patients at every variety of handwork, and literally thousands of articles of artistic and practical merit were shown. That there should be some financial return to the patients, and there was, was quite incidental, but none the less welcome.

Rosenthal also instituted medical staff conferences in all sanatoria and in most of the metropolitan hospitals. The purpose of these, which were held nearly every week, was for the exchange of views between the medical staffs of the Tuberculosis Branch and the chest consultants of the teaching hospitals. At these conferences everybody, from the youngest or newest resident upwards, was free to express his or her views. There was an open invitation to "stick one's neck out". Rosenthal's experience and clarity of thinking were outstanding on these occasions.

His experience of treatment in all its aspects covered every innovation of the last 24 years. He was not always prepared to accept a new "miracle" treatment without question; but once a line of treatment was established, no one could have been more thorough in its application.

It is not possible to detail his numerous activities. He was an enthusiastic worker for the Victorian Tuberculosis Association, of which he was vice-president. He was also president of the Victorian branch of the Laennec Society. He had just completed a paper embodying some of the late effects of pneumonectomy for presentation at the annual meeting of the American College of Chest Physicians, which was held in Vienna late in August, 1960.

One of the outstanding features of his work was the formation of a Gresswell Ex-Patients' Association, a thriving and live organization controlled by the patients themselves. As far as we know, this is a unique body, and no similar one exists or has been alive for so many years.

Rosenthal was deeply interested in music, and periodically gave short talks to the patients over the loud-speaker system on musical appreciation. He was an enthusiastic and competent photographer. After every trip abroad he had an evening of slide-viewing for the patients and friends of the sanatorium, demonstrating his extraordinary facility for producing artistic and unique photographs.

With all this he was one of the most human of men, modest, faithful in friendship and ready to see the other person's pont of view. He had a ready wit and an enviable

sense of humour. David Rosenthal has left us while still at the top of his powers, and it will be difficult to replace him.

The following tribute was spoken by DR. MORRIS C. DAVIS at the funeral service: Today we come here to pay our last tributes and homage to one who by this very gathering has proven his true worth, for David Rosenthal was a loyal friend and a fine colleague. To him this life was a constant challenge—ever presenting with problems to be overcome, an issue to be clarified, a truth to be sought. He burned with an infinite and endless desire for knowledge and a passion for truth. "No drift, nor lie at anchor" for David.

So it was that, had he been spared, he was to have given an authoritative paper in Vienna in three weeks' time which opened up a new field of investigation on the effect of pulmonary disease on the heart. Characteristically this work was carried out on an instrument—an electrocardiograph—chosen by him because of the exciting prospects of knowledge to which it might lead, and presented to him as a tribute from his Gresswell patients.

Headlines meant nothing to him—it was always what lay beneath, and his contant endeavour was for exactness of expression and clarity of thought. Yet he possessed a wonderful sense of humour and a delightful wit. His search was for truth for its own sake, without which no man can be great. Always uneasy lest he be too satisfied, he possessed that rare ability to kindly but firmly remind you that there was always another angle to the problem. To know him

was to admire him, for his was an intellect free from bias, only prepared to resolve the problem when all the facts were known. He possessed the truly open mind with which goes complete tolerance and understanding. He followed in the Maimonides tradition: "Inspire me with true love for this is my art, and let me ever behold in the afflicted and the suffering, only the Human Being."

All were to him equally important. He loved man's weaknesses and his strength, his foolishness and his wisdom, his discord and his harmony. He accepted all as a wonderful colour pattern, ever ready to receive the many component parts so as to weave them into the complete whole. All at Gresswell were inspired by his intellectual honesty, for he asked nothing that he would not do himself. His staff worshipped him.

His love of music and the arts he shared with his friends, and through his magnificent photographic techniques we were all privileged to share in many of his experiences. All will remember the feeling of completeness spent in the lovely evenings at his home. He will be missed by his colleagues, but he will be sorely missed by his patients, for we will never know the amount of good he did; it is to be measured in the thousands of people who now carry on their complete and full life unhampered by the scourge which might have been their lot. By his endeavours, tuberculosis has been reduced to a minor disease. His was a dedication, and if one can measure life with a yard stick of achievement, his calibre is with the giants—and so we shall remember him.

We offer our sympathy to his brother and sister and to all his relatives. With them we shall miss his grand personality. *Vale*, David Braham Rosenthal: "Never more shall we as friends sweet counsel take."

Correspondence.

HYPOGLYCÆMIC EFFECTS OF CHLORPROPAMIDE.

SIR: The conclusions of Dr. D. S. Pryor on the "Hypoglycæmic Effects of Chlorpropamide" as reported in this Journal (October 1) merit comment.

All therapeutic agents can only be regarded as safe when used within the prescribed limits of dosage. It would have been equally appropriate for Dr. Pryor to assert that insulin can cause hypoglycæmia threatening life, and that some types of insulin can produce hypoglycæmia for more than 24 hours after administration.

After three years of experience with the use of chlorpropamide in over 400 patients, I have yet to see dangerous effects when the drug is used in the recommended dosage of not more than 500 mg. per day. The side effects I have observed have been remarkably few—a very occasional "Antabuse"-like effect on taking alcohol and occasional nausea or headache. I regard this drug as probably the most satisfactory of the oral anti-diabetic agents at present available.

Dr. Pryor's case report lacks any detail of chlorpropamide dosage, and the clinical picture was apparently confused by the patient's indulgence in alcohol.

Those unfamiliar with chlorpropamide could gain from one isolated experience a false idea of the value of the drug. My purpose in this letter is to correct any impression that chlorpropamide is in any way dangerous when used with discretion and a proper regard for the recommended limits of dosage.

Yours, etc.,

111 Collins Street, Melbourne.
October 5, 1960.

EWEN DOWNIE.

SIR: I feel the case report of Dr. Pryor (MED. J. AUST., October 1) on the hypoglycæmic effects of chlorpropamide deserves some comment.

It is unfortunate that a report so lacking in clinical and biochemical data gives the impression that chlorpropamide is a dangerous adjuvant in the treatment of diabetes mellitus. I have treated many cases with chorpropamide over the last two years, and have seen no cases of serious hypoglycæmia, even in the early experimental days when double the now advised dosage was used.

I presume that Dr. Pryor was not aware that chlorpropamide is slowly excreted, and therefore did not take appropriate measures to counteract the hypoglycæmia. Adequate quantities of carbohydrate and protein orally, in adidtion to intravenous glucose, would have prevented any relapse.

In my opinion, chlorpropamide is probably the most useful of the oral tablets at present available, and correctly administered causes no ill-effects.

Yours, etc.,

Diabetic Clinic,
Prince Henry's Hospital,
Melbourne.
October 6, 1960.

JOHN R. STAWELL.

TRAUMATIC RUPTURE OF THE SPLEEN.

SIR: Mr. J. B. Binks should be congratulated on his lucid exposition on the subject of "Traumatic Rupture of the Spleen", and on his success in a personal series of 10 cases (MED. J. AUST., September 3, 1960, page 374). His description of the operation, as he performs it, is interesting, and in his hands it is evidently effective. But I cannot refrain from expressing disagreement with the method he advocates.

As he describes it, this comprises retraction of the left costal margin; emptying the stomach through a wide-bore stomach tube; retraction of the stomach and the intestines; clearing away all free blood and clot and loose splenic fragments; then "once a perfect view with bowel, stomach and blood out of the way has been obtained, the rest is easy. The spleen is grasped and held towards the mid-line, which allows the parietal peritoneum on the side to be snipped with long scissors". Then clamps are applied close to the hilum and the spleen is removed.

I feel sure this method entails unnecessary difficulty and delay in the performance of this operation, and in the hands of less experienced surgeons it could be highly dangerous. In 1952, I reported[1] a personal series of 13 cases of splenectomy for rupture, and described an operative procedure which I consider superior:

> There is no need to visualize the spleen or its pedicle *in situ* at all, and it is dangerous to attempt to do so. Pass a hand over the spleen, and feel it carefully, and the blood clot and the torn surface can always be detected if present. Then the lieno-renal ligament is broken through with the fingers, and the spleen is lifted forwards and to the right towards its pedicle. By this means, it can be delivered safely out of the wound—even a right paramedian incision—and it is only then one should expect the spleen and its pedicle to come into view.

There was only one death in this series—from a pressure pneumothorax which was overlooked.

In 1954, Ruscoe Clarke,[2] writing from his vast experience at the Birmingham Accident Hospital, commented as follows:

> The technique of removing a ruptured spleen differs from that of removing a spleen which is the site of long-standing disease. The approach described by Lawson (1952) I have practised for many years".

He then quoted verbatim the description I have given above, adding: "This technique saves many valuable minutes in delivering the spleen and controlling the bleeding".

Since 1952, I have myself performed splenectomy for rupture in another 13 cases, all by the same method and without fatality.

Therefore, I feel it is inappropriate for Mr. Binks to refer disparagingly to this method as a "game of lucky dip". If this comment is allowed to pass without dispute, it will discourage surgeons from employing what I regard as correct technique in these circumstances. It has the cardinal virtues of speed and simplicity, and in my opinion it is the safest procedure in the performance of this emergency operation.

Yours, etc.,

85 Spring Street,
Melbourne.
October 4, 1960.

ROBERT S. LAWSON.

[1] MED. J. AUST., 1952, 2:396 (September 20).
[2] *Lancet*, 1954, 2:877 (October 30).

Royal Australasian College of Surgeons.

PRIMARY EXAMINATION FOR FELLOWSHIP.

A PRIMARY EXAMINATION in anatomy (including normal histology) and applied physiology and the principles of pathology will be conducted in Melbourne in March, 1961, for the fellowship of the Royal Australasian College of Surgeons. The written papers will be held on Thursday and Friday, March 2 and 3, 1961. The viva-voce sections of the examination will commence on Monday, March 6, 1961. The examination is reciprocal with the primary examination for fellowship of the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh and the Royal College of Surgeons in Ireland, or the primary examination in surgery of the Royal Faculty of Physicians and Surgeons of Glasgow and The College of Physicians, Surgeons and Gynæcologists of South Africa. Each examination is open to graduates of not less than one year's standing of a medical school approved by the Council of the College for the purpose.

Candidates must submit evidence of their qualifications and date of acquirement thereof. Forms of application for admission to the examination may be obtained from the Examination Secretary, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1, Victoria. The fee for admission or readmission to the examination is £31 10s., plus exchange on cheques drawn on banks outside Melbourne. The fee must oe forwarded with the form of application so as to reach the Examination Secretary at his office in Melbourne not later than January 20, 1961. It is stressed that the entries close at the College office in Melbourne on January 20, 1961, and that late entries cannot be accepted. Copies of the regulations governing examinations for fellowship are available on application.

FACULTY OF ANÆSTHETISTS.

Primary Examinations for Fellowship.

A PRIMARY EXAMINATION in anatomy, physiology, pharmacology and pathology will be conducted in Melbourne in March, 1961, for the fellowship of the Faculty of Anæsthetists of the Royal Australasian College of Surgeons. The written papers will be held on Thursday and Friday, March 2 and 3, 1961. The viva-voce sections of the examinations will commence on Monday, March 6, 1961. The examination is reciprocal with the primary examination for fellowship of the Faculty of Anæsthetists of the Royal College of Surgeons of England. Each examination is open to graduates of not less than one year's standing of a medical school approved by the Council of the College for the purpose.

Candidates must submit evidence of their qualifications and date of acquirement thereof. Forms of application for admission to the examination may be obtained from the Examination Secretary, Faculty of Anæsthetists, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1, Victoria.

The fee for admission or readmission to the examination is £31 10s., plus exchange on cheques drawn on banks outside Melbourne. The fee must be forwarded with the form of application so as to reach the Examination Secretary at his office in Melbourne not later than January 20, 1961. It is stressed that entries close at the Faculty office in Melbourne on January 20, 1961, and that late entries cannot be accepted. Copies of the regulations governing examinations for fellowship are available on application.

Naval, Military and Air Force.

APPOINTMENTS.

THE following appointments, changes, etc., are published in the *Commonwealth of Australia Gazette*, No. 66, of September 29, 1960.

NAVAL FORCES OF THE COMMONWEALTH.

Citizen Naval Forces of the Commonwealth.

Royal Australian Naval Reserve.

Appointment.—James Estcourt Hughes is appointed Honorary Surgeon Captain, dated 1st September, 1960.

Retirement.—Surgeon Commander James Estcourt Hughes is retired from the Royal Australian Naval Reserve, dated 31st August, 1960.

Royal Australian Naval Volunteer Reserve.

Appointment.—Sydney Lance Townsend is appointed Honorary Surgeon Captain, dated 1st September, 1960.

Promotion.—Surgeon Lieutenant-Commander Russell Geoffrey Cole is promoted to the rank of Surgeon Commander, dated 1st September, 1960.

Retirement.—Surgeon Commander Sydney Lance Townsend is retired from the Active List, dated 31st August, 1960.—(Ex. Min. No. 56—Approved, 24th September, 1960.)

AUSTRALIAN MILITARY FORCES.

Citizen Military Forces.

Southern Command.

Royal Australian Army Medical Corps (Medical).—3/50312 Major A. V. Jackson is appointed from the Reserve of Officers, and is appointed Assistant Director General of Medical Services, Consultant Pathologist, Directorate of Medical Services Army Headquarters, and to be Lieutenant-Colonel (Temporary Colonel), 18th August, 1960. 3/82241 Lieutenant-Colonel D. C. Cowling relinquishes command 6th Field Ambulance, 30th April, 1960. *To be Colonel, 1st July, 1960*—4/31963 Lieutenant-Colonel (Temporary Colonel) V. D. Plueckhahn.

Central Command.

Royal Australian Army Medical Corps (Medical).—4/31905 Lieutenant-Colonel G. W. E. Aitken relinquishes the appointment of Commanding Officer, 1st Casualty Clearing Station, 30th June, 1960. The following officers are transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Central Command), 1st July, 1960:—4/31911 Lieutenant-Colonel F. E. Welch, E.D. and 4/32064 Major R. S. Colton. *To be Temporary Lieutenant-Colonel, 1st July, 1960*—4/32070 Major A. K. Grant. *To be Temporary Major, 1st July, 1960*—4/32112 Captain R. Hecker.

Reserve Citizen Military Forces.

Eastern Command.—The following officers are placed upon the Retired List (Eastern Command) and are granted military titles equivalent to the substantive or honorary rank shown, with permission to wear the prescribed uniform:

Majors C. B. Cox and R. T. Dalton, and Captain L. E. Odlum, 31st October, 1959; Captains W. N. Newton and W. S. Williamson, 31st December, 1959, and Honorary Captain D. G. Mackellar, 31st August, 1960.

The World Medical Association.

FOURTEENTH GENERAL ASSEMBLY.

Election of Officers.

AT its fourteenth general assembly held in West Berlin, Germany, on September 15 to 22, 1960, the World Medical Association elected the following officers: *President*, 1960-1961: Dr. Paul Eckel (Germany). *President-Elect*, 1960-1961: Dr. Antonio Moniz Aragao (Brazil). *Members of Council*, 1960-1963: Dr. J. G. Hunter (Australia), Dr. L. W. Larson (U.S.A.), Dr. Antonio Spinelli (Italy), Dr. Hector Rodriguez H. (Chile). *Secretary-General*, 1961: Dr. Heinz Lord.

The Council of the World Medical Association elected the following officers for the coming year: *Chairman of Council*, Dr. Gunnar Gundersen (U.S.A.), *Vice-Chairman of Council*, Dr. Felix Worré (Luxembourg). *Executive Editor, World Medical Journal*, Dr. Stanley S. B. Gilder (U.K.); *Associate Editor*, Dr. J. R. Gosset (France).

The officers of committees for 1960-1961 include: *International Liaison*: Dr. Jean Maystre (Switzerland). *Medical*

Education: Dr. L. W. Larson (U.S.A.). *Medical Ethics*: Dr. Hugh Clegg (U.K.). *Planning and Finance*: Dr. T. C. Routley (Canada), Chairman, Dr. L. R. Mallen (Australia), Vice-Chairman. *Socio-Medical Affairs*: Dr. Felix Worré (Luxembourg), Chairman, Dr. Rolf Schlögell (Germany), Secretary. *Liaison Officers*: Dr. Jean Maystre (Switzerland), Dr. Charles Jacobsen (Denmark).

Post-Graduate Work.

THE MELBOURNE MEDICAL POST-GRADUATE COMMITTEE.

PROGRAMME FOR NOVEMBER, 1960.

Country Courses.

Portland.—On November 5, at the District Hospital, Portland, the following course will be given: 3.45 p.m., "Recent Advances in Cardiology", Dr. H. B. Kay; 5.15 p.m., "Non-Malignant Conditions of the Breast", Mr. J. Freidin. The local secretary is Dr. R. R. Sobey, 6 Spence Street, Warrnambool.

Traralgon.—On November 12, at the District Hospital, Traralgon, the following course wil be given: 2.30 p.m., "The Coughing Child", Dr. H. N. B. Wettenhall; 4.15 p.m., "Intravenous Therapy in Children", Dr. Max Robinson; 8 p.m., "Chronic Pyuria in Children", Mr. F. D. Stephens. The local secretary is Dr. J. E. Joseph, 237 Princes Highway, Morwell.

Bendigo.—On November 12, at the Northern District School of Nursing, Lister House, Rowan Street, Bendigo, the following course will be given: 2 p.m., "Orthopædic Deformities in Children", Dr. Murray Clarke; 3 p.m., "Current Concepts of Steroid Therapy", Dr. H. Pincus Taft; 4.30 p.m., "Chronic Leg Ulceration", Mr. S. F. Reid. The local secretary is Dr. M. Clark, 98 Mitchell Street, Bendigo.

Mooroopna.—On November 19, at the Mooroopna Base Hospital, the following course will be given: 2.15 p.m., "The Use of Unmodified Blood Given by Direct Transfusion", Dr. John McLean; 4.15 p.m., "Early Recognition of Abdominal Cancer", Mr. Howard Eddey; 5.45 p.m., "Alcohol and Road Accidents", Dr. John Birrell. The local secretary is Dr. B. R. Schloeffel, Orr Street, Shepparton.

Ballarat.—On November 24, at Craig's Hotel, at Ballarat, at 8 p.m., Dr. Donald Duffy will discuss "Renal Disease". The local secretary is Dr. I. C. Goy, 22 Rippon Street, Ballarat.

FEES.—The fees for the foregoing courses are at the rate of 15s. per session, but those who have paid an annual subscription to the Committee are invited without further charge.

Flinders Naval Depot.

On November 16, at Flinders Naval Depot, at 2.30 p.m., Mr. K. C. Bradley will discuss "Pain Mechanisms". This lecture is being given by arrangement with the Royal Australian Navy.

Overseas Visitor.

Professor G. M. Wilson, Professor of Pharmacology and Therapeutics, Sheffield, will visit Melbourne from November 19 to 27. The Committee is arranging for him to visit the Royal Melbourne Hospital, the Alfred Hospital, St. Vincent's Hospital, the Royal Children's Hospital and the Royal Women's Hospital, and information in this regard may be obtained from the Director. Professor Wilson is an outstanding medical investigator, whose interests mainly lie in the endocrinological field.

INFORMATION.

The address of the Melbourne Medical Postgraduate Committee is 394 Albert Street, East Melbourne. Telephone: FB 2547.

ST. VINCENT'S HOSPITAL, SYDNEY: GASTRO-ENTEROLOGY UNIT.

A MEETING of the Gastro-Enterology Unit of St. Vincent's Hospital, Sydney, will be held on Thursday, October 27, at 5.30 p.m. Several interesting cases will be presented. All medical practitioners are invited to attend.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 17, 1960.[a]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	1	3(3)	..	1	..	..	..	5
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	3	..	8(1)	..	..	..	6	..	17
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	1	12(10)	2(2)	..	..	1	6	..	22
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	1(1)	..	1(1)	1	..	1	1	5
Encephalitis	2	1(1)	..	..	..	..	..	..	3
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	97(49)	53(38)	18(5)	8(4)	6(3)	..	..	2	184
Lead Poisoning	..	..	3	..	..	..	..	..	3
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	1(1)	..	..	..	..	..	1
Meningococcal Infection	2(1)	1(1)	..	..	..	..	..	..	3
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	1	..	..	1	..	..	2
Puerperal Fever	2	..	1	..	..	..	..	..	3
Rubella	..	11(8)	..	..	1(1)	..	..	..	12
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	9(3)	22(13)	5(3)	4(1)	1	1	..	..	42
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	..	..	..	..	1
Trachoma	..	..	..	..	2	..	5	..	7
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	21(15)	21(17)	26(17)	1	10(4)	2(1)	6	..	87
Typhoid Fever	1(1)	..	..	..	..	..	..	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[a] Figures in parentheses are those for the metropolitan area.

SURGICAL SEMINAR AT ST. VINCENT'S HOSPITAL, SYDNEY.

A SURGICAL SEMINAR will be held at St. Vincent's Hospital, Sydney, on Monday, October 31, 1960, at 5.15 p.m., in the lecture hall on the fifth floor. A paper entitled "Surgery of the Colon and Rectum at St. Vincent's Hospital" will be read by Mr. P. J. Kenny.

INSTITUTE OF CLINICAL PATHOLOGY AND MEDICAL RESEARCH AND LIDCOMBE STATE HOSPITAL.

Weekly Seminars.

THE following subjects have been chosen for the programme of weekly seminars which have been arranged by the staff of Lidcombe State Hospital, in conjunction with the Institute of Clinical Pathology and Medical Research, Lidcombe. This list completes the programme for 1960, and it is expected that seminars will recommence in February, 1960. As previously, each meeting will commence at 3.30 p.m., in the Lecture Hall of the Institute, which is situated in the grounds of Lidcombe State Hospital. All medical practitioners and interested ancillary staff are invited to attend.

October 24: "Deaths under Anæsthesia", Dr. R. Holland, Lidcombe State Hospital.

October 31: Symposium on "The Control of Anticoagulant Therapy", Dr. Barbara Arnold and Mr. H. Lawson-Smith, Institute of Clinical Pathology, and Dr. G. C. Hughes, Lidcombe State Hospital.

November 7: "Rheumatoid Arthritis", Dr. G. Kellerman, Lidcombe State Hospital.

November 14: "Recent Technical Innovations in Biochemistry", Dr. R. N. Beale, Mr. D. Croft, Mr. J. Bostrom and Mr. R. Taylor, Institute of Clinical Pathology.

November 21: "Chemotherapy in Modern Psychiatry", Dr. B. S. Stephen, Lidcombe State Hospital.

November 28: "General-Practitioner-Hospital Relationships", Guest Speaker, Dr. Keith Mallett, general practitioner, Rosebery.

December 5: "Microcinematography of Living Cells" (with film), Dr. H. Kramer, Director, Institute of Clinical Pathology.

December 12: symposium on "Chemotherapy of Tuberculosis", Dr. W. Tellesson, Randwick Chest Hospital, and Dr. D. Hansman and Mr. B. O'Connor, Institute of Clinical Pathology.

Notes and News.

Summer Camp for Diabetic Children.

The Association of Summer Camps for Diabetic Children announces that the annual camp will be held from January 14 to 28, 1961, at the Fairbridge Farm School, Molong, N.S.W. Any diabetic boy or girl between the ages of six and 11 years is eligible to attend. The camp will be under the supervision of a qualified medical staff. Information may be obtained from the Honorary Secretary, Miss R. Pirie, c.o. Dietitian's Office, Royal North Shore Hospital, St. Leonards. Telephone: JF 0411, extension 302.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Wong-See, Jenson Junn-Sing, M.B., B.S., 1957 (Univ. Sydney), 70 David Street, Turner, A.C.T.

Babajews, Alibaba, M.D., 1937 (Univ. Baku) Registered under Section 21c (4) of the *Medical Practitioners Act*, 1938-1958, St. Joseph's Hospital, Auburn.

The undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association:

Limmer, Alan Noel, M.B., B.S., 1958 (Univ. Adelaide), 10 Dequettville Terrace, Kent Town, Adelaide.

Diary for the Month.

OCTOBER 25.—Tasmanian Branch, B.M.A.: Southern Subdivision.
OCTOBER 25.—New South Wales Branch, B.M.A.: Hospitals Committee.
OCTOBER 26.—Victorian Branch, B.M.A.: Branch Council.
OCTOBER 27.—Tasmanian Branch, B.M.A.: Northern Subdivision.
OCTOBER 27.—South Australian Branch, B.M.A.: Scientific Meeting.
OCTOBER 28.—Queensland Branch, B.M.A.: Council Meeting.
OCTOBER 29.—New South Wales Branch, B.M.A.: Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

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